Twice a Day, Twice the Ease: Simplifying Nephropathic Cystinosis Treatment

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Disclosures

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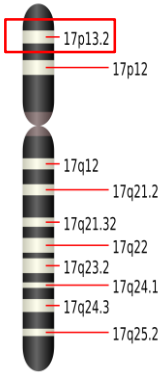
- Chiesi, Cystinosis Research Foundation, Else Kröner-Fresenius-Stiftung, German Research Foundation, and Kyowa Kirin

Speaker fees/consultancy

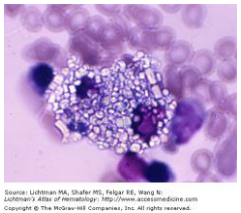
- Advicenne, Biologix, Chiesi, Kyowa Kirin, Medison Pharma, Recordati Rare Diseases, and Ultragenyx

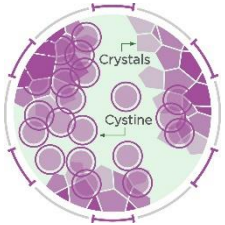
Nephropathic cystinosis

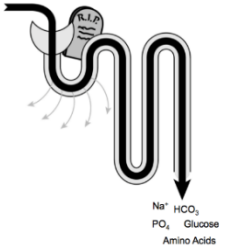
- An autosomal recessive disease caused by lysosomal accumulation of cystine due to defective exodus of cystine out of the lysosomes
- Lysosomal cystinosin (*CTNS*, 17p13) is mutated in cystinosis
- Incidence ~1:100,000 - 200,000 newborns
- Most common cause of inherited renal Fanconi syndrome progressing to kidney failure (if untreated) around the age of 10 years



Macrophage with cystine crytals



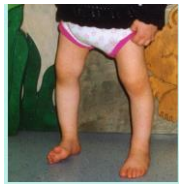
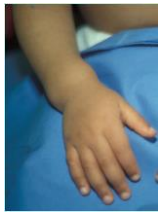
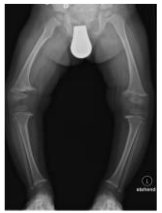
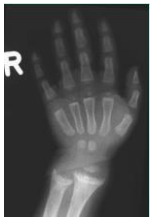
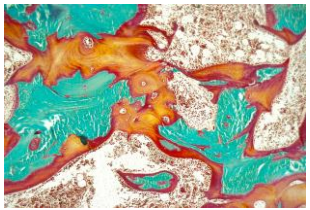




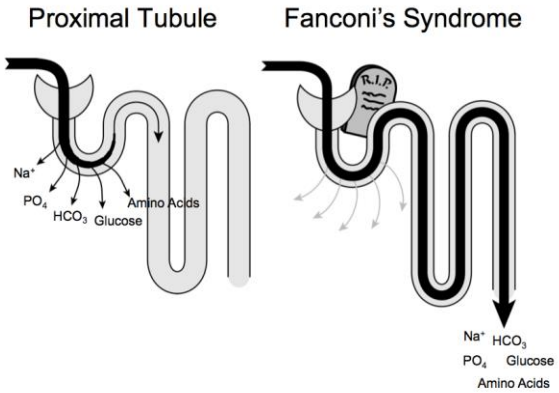
Town et al. Nat Genet 1998; Attard et al. Hum Mol Genet 1999
Kalatzis et al. Hum Mol Genet 2004; Levtchenko et al. Eur J Hum Genet 2014;
Emma F et al. Kidney Int. 2021

Diagnosis of cystinosis

- **Suspected clinical presentation**
  – Failure to thrive, polyuria, polydipsia, dehydration, fever episodes, rickets

due to renal Fanconi syndrome (maybe incomplete at the beginning)



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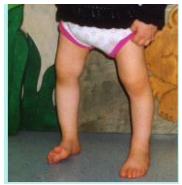
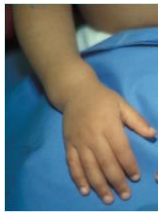
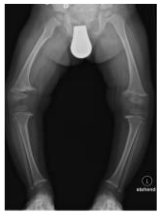
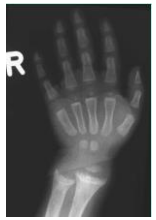
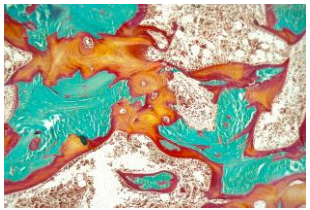






due to renal Fanconi syndrome (maybe incomplete at the beginning)

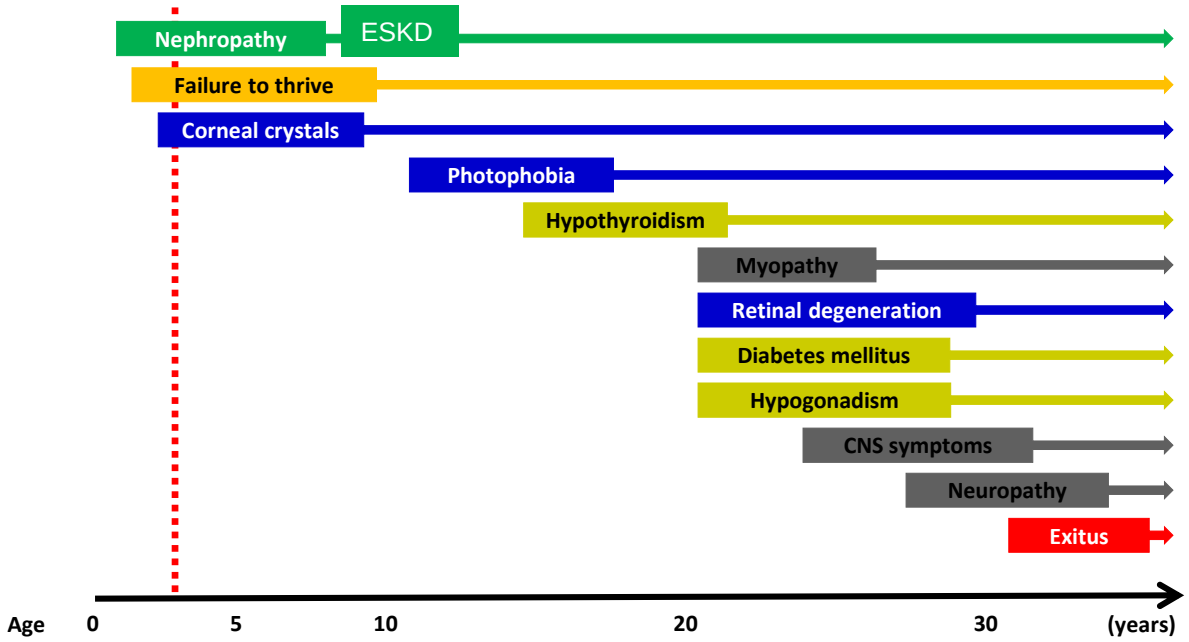
- **Measurement of elevated cystine content in leukocytes:**
  – Patients at diagnosis > 2 nmol ½ cystine/mg protein
  – Controls < 0.3 nmol ½ cystine/mg protein
  – Heterozygotes < 1 nmol ½ cystine/mg protein

- **Cystine crystals in cornea (>1 year)**
- **Molecular analysis of cystinosis gene**

Corneal cystine crystals

Cystinosis: natural history in untreated patients

Clinical manifestations of cystinosis in patients not treated with cysteamine[1]



CNS, central nervous system; ESKD, end-stage chronic kidney disease

Adapted from Ariceta G, et al. *Nefrologia*. 2015.[1]

Courtesy of Francesco Emma

Treatment of cystinosis

Symptomatic

- Free access to water
- Nutrition: adequate caloric, protein, and calcium intake = 100% SDI (suggested dietary intake)
  - Dietician, tube feeding / PEG in young children
- Replacement of electrolytes, phosphate, and alkali
- Active vitamin D (1α calcidiol or calcitriol) in <u>combination</u> with phosphate supplements
- Vitamin D supplementation (if required)

Emma *et al.* NDT 2012; Veys *et al.* Curr Opin Pediatr 2017; Drube *et al.* Nat Rev Nephrol 2019
Hohenfellner *et al.* J Inher Metab Disease 2019; Lahring *et al.* JCEM 2024

Treatment of cystinosis

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- Replacement of electrolytes, phosphate, and alkali
- Active vitamin D (1α calcidiol or calcitriol) in combination with phosphate supplements
- Vitamin D supplementation (if required)
- Indomethacin to decrease diuresis and electrolyte losses (if required)
- RAS inhibitors in case of proteinuria (>1 g/g creatinine)
- Growth hormone in children with persistent poor growth
- Hormone replacement therapy for hypothyroidism, hypogonadism (male), and diabetes
- Male: percutaneous epididymal sperm asservation and sperm cryopreservation

Emma *et al.* NDT 2012; Veys *et al.* Curr Opin Pediatr 2017; Drube *et al.* Nat Rev Nephrol 2019
Hohenfellner *et al.* J Inher Metab Disease 2019; Lahring *et al.* JCEM 2024

Treatment of cystinosis

Specific treatment with cysteamine

- Depletes intra-cellular cystine accumulation
- Life long treatment
- Must be continued after kidney transplantation
- **Systemic**: **1.3** - 1.95 g/m² BSA

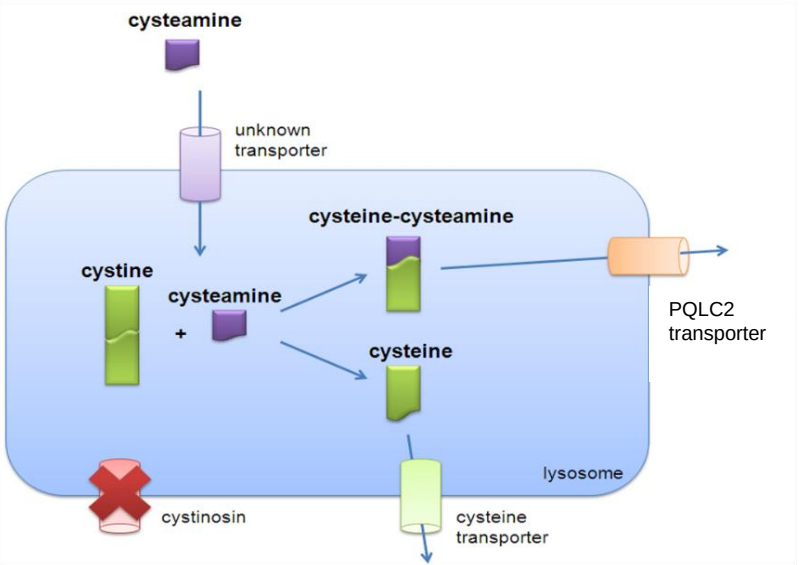
  Immediate release: Cystagon®, every 6h

  Delayed release: Procysbi®, every 12h

  Target: leukocyte cystine levels < 1.0 nmol ½ cystine/mg protein
- **Topical** for corneal depositions:

  0.5% eye drops every 1-2h

  0.55% gel formulation (Cystadrops®), every 6h



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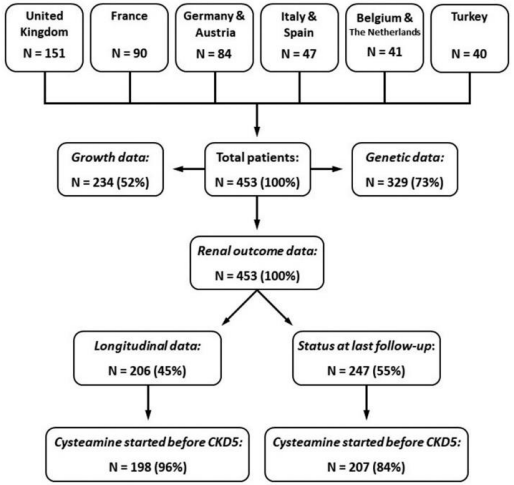
Hohenfellner *et al.* J Inher Metab Disease 2019; Lahring *et al.* JCEM 2024

Improving kidney prognosis

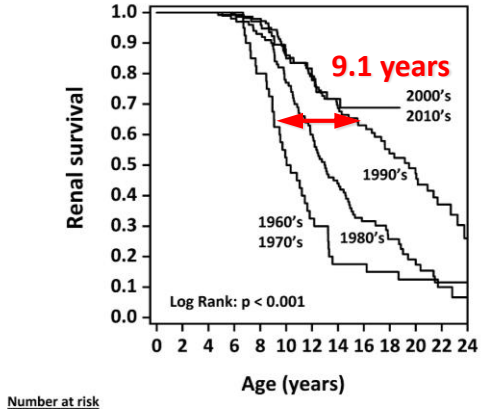
- Prevent developing kidney failure
- Prevent or reverse Fanconi syndrome

European cohort

Study design[1]



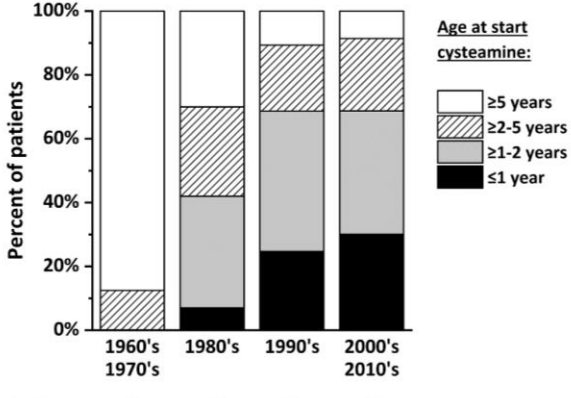
Survival function for patients divided per decade of birth[1]



Number at risk

1960's - 1970's:	40	39	32	13	7	5	2
1980's:	100	99	93	60	28	10	4
1990's:	150	148	139	87	51	27	6
2000's - 2010's:	163	135	84	40	12		

Age at which cysteamine therapy was prescribed[1]



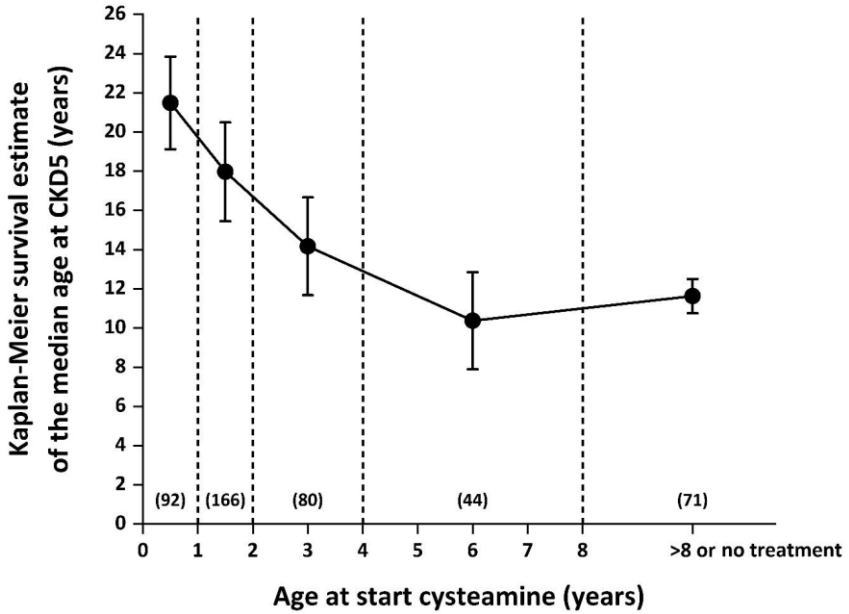
Number of patients	40	100	150	163

CKD5, stage 5 chronic kidney disease.

1. Emma F, et al. *Kidney Int*. 2021;100(5):1112–1123.

Source and adapted from Emma F, et al. 2021.[1]

Age at dialysis according to the age at starting cysteamine



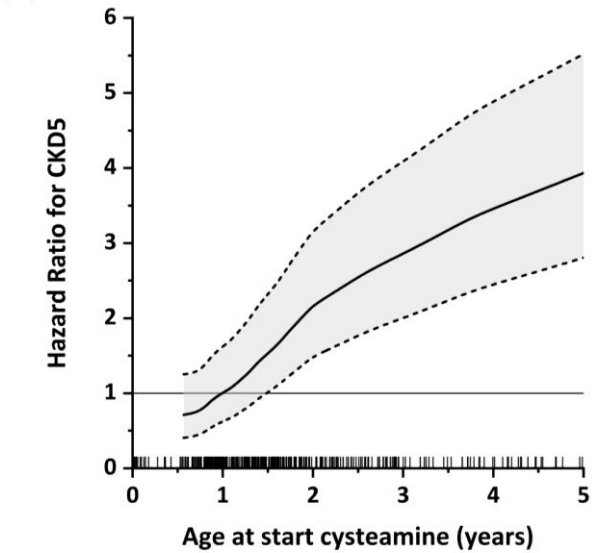
CKD5, stage 5 chronic kidney disease.

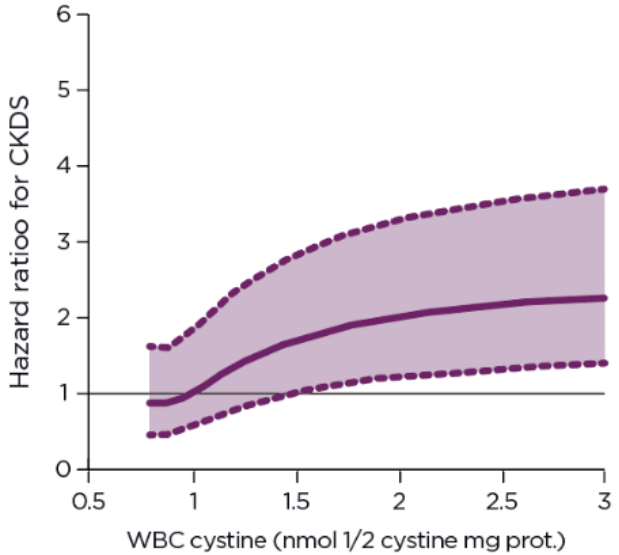
1. Emma F, et al. *Kidney Int.* 2021;100(5):1112–1123 and supplementary data.

Adapted from Emma F, et al. 2021.[1]

Cysteamine therapy and kidney function outcome

Impact of cysteamine therapy on the risk of progressing to end-stage kidney disease*[1]

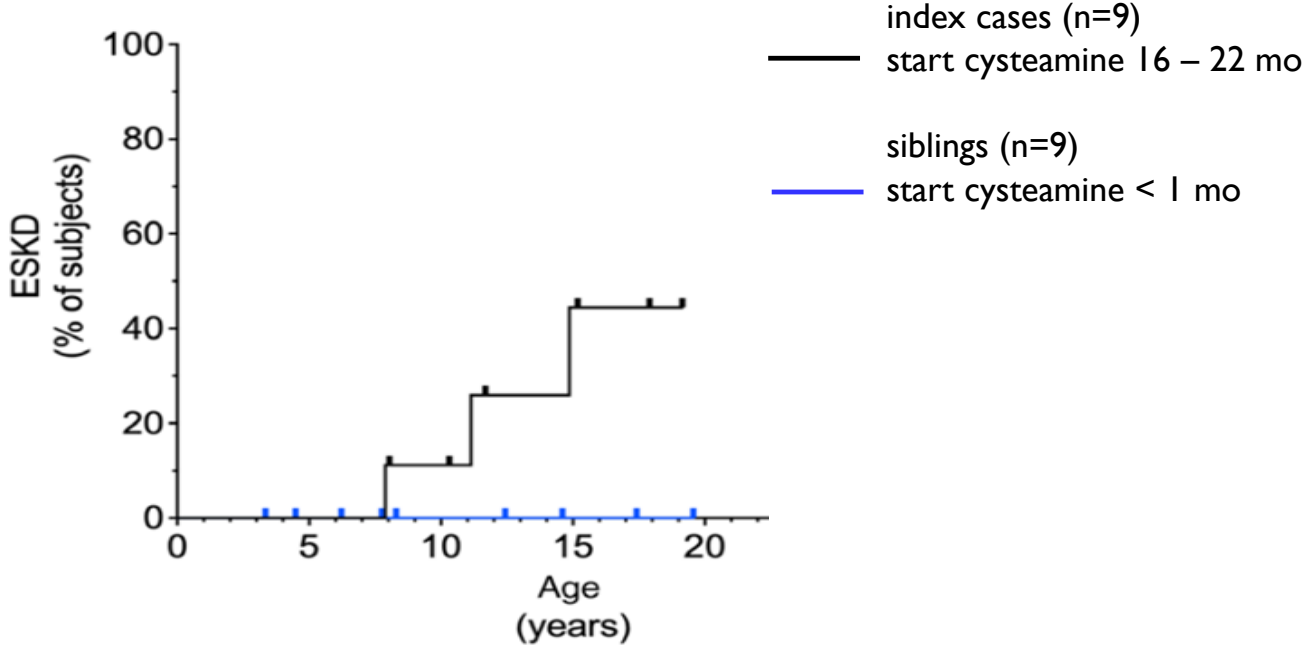




*Shaded areas indicate the 95% confidence intervals of the hazard ratio; vertical bars at the bottom of the graphs indicate individual patients. Only patients that had started cysteamine before the age of 8 years were included in this analysis.
CKD5, stage 5 chronic kidney disease.
1. Emma F, et al. *Kidney Int.* 2021;100(5):1112–1123.

Source: Emma F, et al. 2021.[1]

Starting cysteamine at birth prevents ESKD in siblings of cystinosis patients



Veys *et al.* JIMD 2022

Effect of early cysteamine on renal Fanconi syndrome

n = 6 cystinosis patients treated with cysteamine **< 2 mo** of age

Patient #	**105**	**88**	**5**	**74**	**8**	**99**
Age (y-mo)	2-7	4-2	16-7	10-9	18-7	6-5
Oral replacement						
Potassium	No	No	No	No	Yes	Yes
Bicarbonate	No	No	No	No	Yes	Yes
Citrate	No	No	No	No	No	Yes
Phosphate	No	No	No	No	Yes	Yes

Hohenfellner *et al.* Mol Genet Metab 2023

Extrarenal symptoms: French study in 86 adults

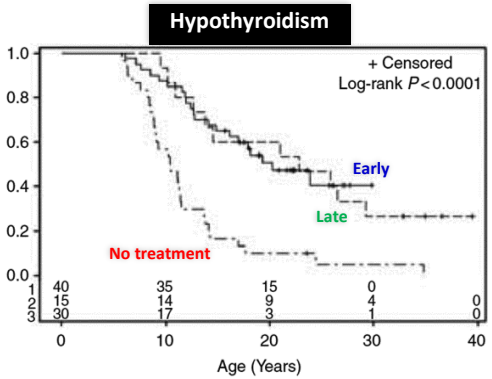
Survival curves

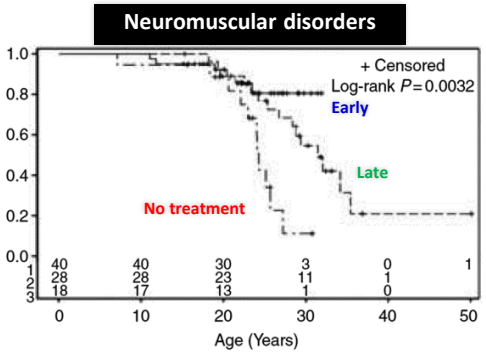
Age when cysteamine was started

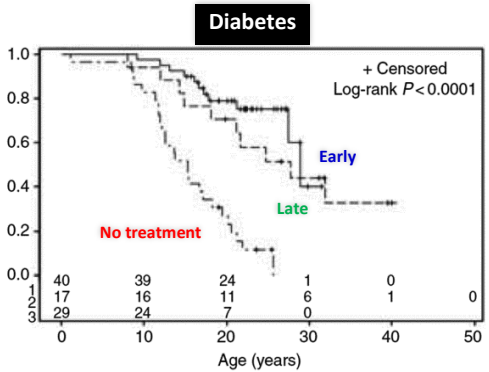
Early: 0–4 years N = 40

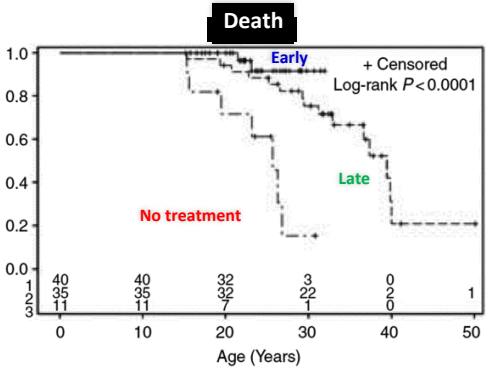
Late: >5 years N = 8

No treatment N = 38





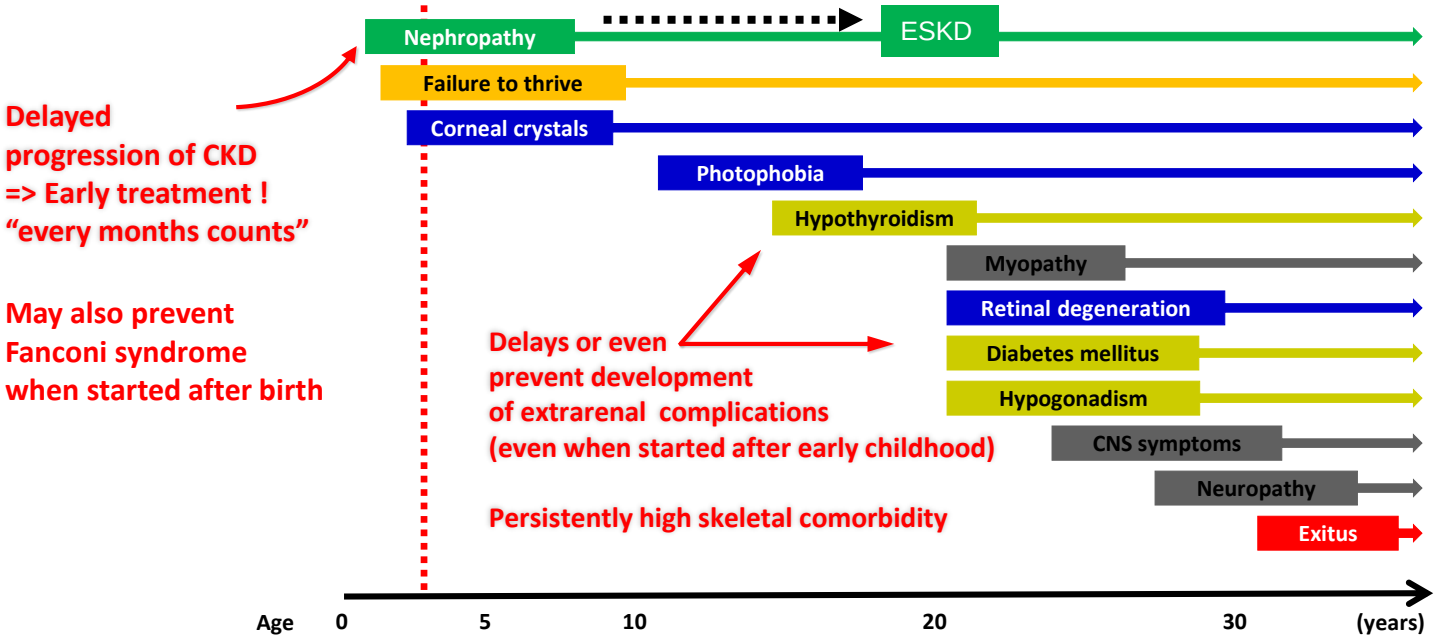




Adapted from Brodin-Sartorius A, et al. 2012

Cystinosis: impact of cysteamine treatment

Clinical manifestations of cystinosis[1,2,3,4]



CNS, central nervous system;
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Emma F, et al. *Kidney Int.* 2021 [2]
Brodin-Sartorius A, et al. *Kidney Int.* 2012 [3]

Veys K, et al. J Inherit Metab Dis. 2023 [4]
Hohenfellner et al. Mol Genet Metab 2023[5]

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NEPHROLOGY ROUNDS

Pregnancy and Breastfeeding in Nephropathic Cystinosis With Native Kidneys

Check for updates

Lillian Chan[1], Jenny Wichart[2], Tony Kiang[3], Rshmi Khurana[1,4], Jon A. Gangoiti[5], Bruce A. Barshop[5] and Julian Midgley[6]

[1]Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; [2]Department of Pharmacy, Alberta Health Services, Calgary, Alberta, Canada; [3]Translational Pharmacotherapy, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada; [4]Department of Obstetrics & Gynecology, Women and Children's Health Research Institute, University of Alberta, Edmonton, Alberta, Canada; [5]Biochemical Genetics and Metabolomics Laboratory, Department of Pediatrics, University of California, San Diego, California, USA; and [6]Department of Pediatrics, University of Calgary, Calgary, Alberta, Canada

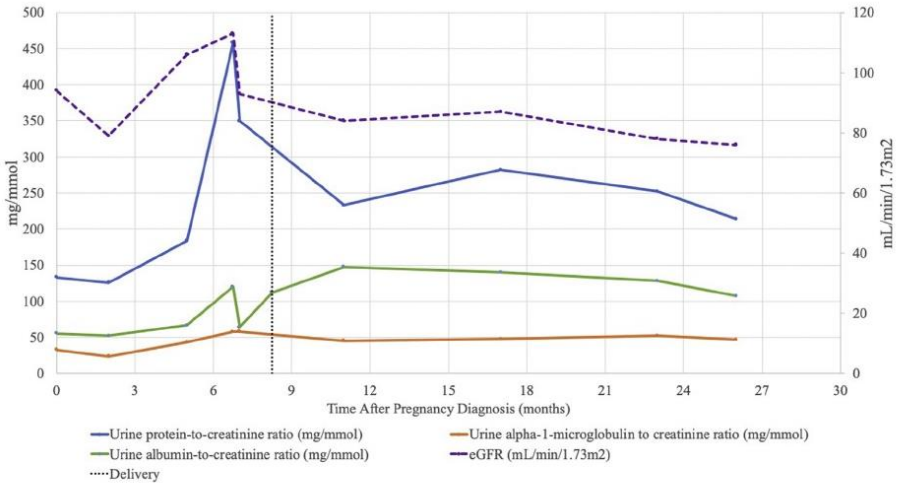


Figure 1. Urinary proteins and eGFR at baseline, during pregnancy and postpartum. eGFR, estimated glomerular filtration rate.

Table 1. Breastmilk cysteamine concentration relative to dose of delayed-release cysteamine bitartrate at steady state

Time postdose (h)	Breastmilk cysteamine concentration (mg/l)
0	0.12
2	0.76
4	1.87
6	0.51

The calculated relative infant dose was 0.4%.

The predicted infant cysteamine dose over 24 hours was 0.52 mg.

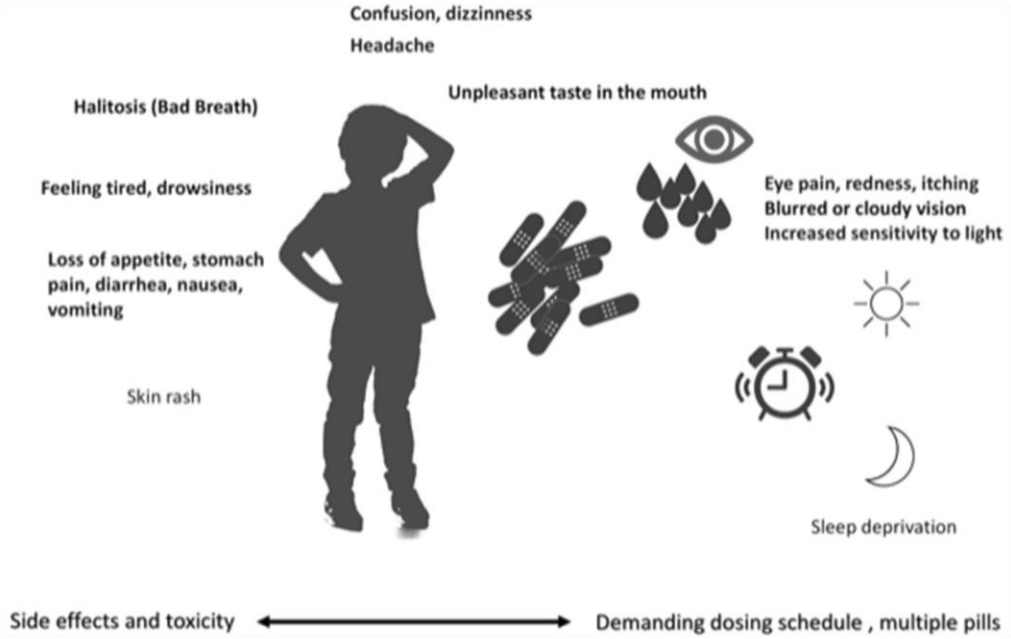
Chan C. et al, Kidney Int Rep (2022) 7, 1716–1719

Pediatric Nephrology (2024) 39:2861–2874
https://doi.org/10.1007/s00467-024-06345-1

REVIEW

Addressing the psychosocial aspects of transition to adult care in patients with cystinosis

Stella Stabouli[1] · Anna Sommer[2] · Stefanie Kraft[2] · Katharina Schweer[2] · Dirk Bethe[3] · Aurelia Bertholet-Thomas[4] · Suzanne Batte[5] · Gema Ariceta[6] · Sandra Brengmann[7] · Justine Bacchetta[4] · Francesco Emma[8] · Elena Levtchenko[9] · Rezan Topaloglu[10] · Lore Willem[11] · Dieter Haffner[12] · Jun Oh[2]



Adherence to Cysteamine Therapy Among Patients Diagnosed with Cystinosis in Saudi Arabia: A Prospective Cohort Study

Reem Algasem [1], Nedaa Zainy [1], Essam Alsabban [2], Hamad Almojalli [3], Khalid Alhasan [3], Tariq Ali [3], Deiter Broering [3] and Hassan Aleid [3,*]

Table 1. Baseline characteristics of the participants (n = 25) of the study.

	Mean + SD *
Age (years)	19.04 + 6.78
Weights (Kg)	41.3 + 14.09
Height (cm)	137.74 + 18.12
	N (%)
Gender	
Male	9 (36)
Female	16 (64)
Cysteamine therapy	
Oral (IR)	23 (92)
Eye drops	13 (52)

* SD—Standard Deviation.

Morisky Medication Adherance Scale

Medication Possession Ratio

Health Survey (SF-36)

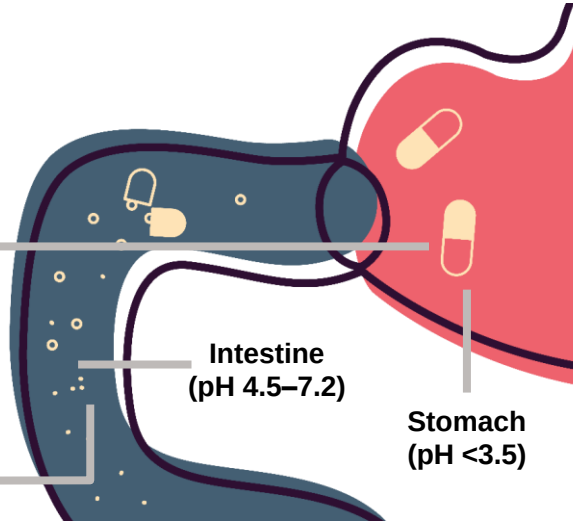
- IR cysteamine: 26% of patients were highly adherant; 46% of patients showed a median level of adherance
- Cysteamine eye drops: 40% of patients were highly adherant; 33% showed a median level of adherance
- QoL affected in the domains of ‘social functioning’ and ‘energy/fatigue’

⇒ Sub-optimal adherence to IR cysteamine and cysteamine eye drops in patients from Saudi Arabia

Proprietary, enteric-coated microgranule technology of PROCYSBI

PROCYSBI gelatin capsules (25 mg or 75 mg)[1–3]

Gelatin dissolves in the stomach releasing the microgranules



The enteric coating of each microgranule is designed to bypass the stomach and dissolve at higher pH (e.g. intestine)[2]

Figure developed by Chiesi, based on information from the European patent.[2]

- **At pH above 5.5, the microgranules dissolve, releasing cysteamine powder into the intestine[4]**
- **Each microgranule has a different thickness enteric coating → differential dissolution in small intestine[2]**
- **This provides the delayed and extended release of cysteamine[1,2]**

1. Langman CB, et al. Clin J Am Soc Nephrol 2012;7:1112–1120 [Erratum in Clin J Am Soc Nephrol. 2013;8:468]; **2.** European patent office, PROCYSBI patent EU EP1919458A2, 2012; **3.** PROCYSBI EU Summary of Product Characteristics. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002465/WC500151313.pdf; **4.** Dohil R and Rioux P. Clin Pharmacol Drug Devel 2013;2:178–185.

Delayed-release PROCYSBI can be dosed 12 hourly[1]

PROCYSBI provides 12 hours of cystine control, enabling twice-daily dosing[1]

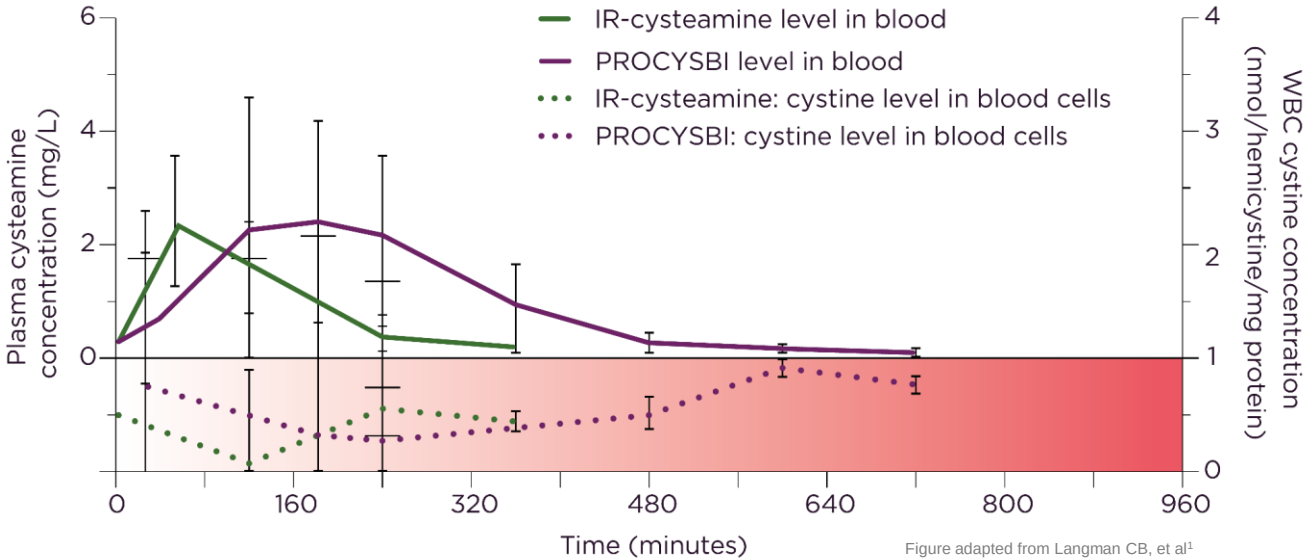


Figure adapted from Langman CB, et al[1]

- This RCT compared PROCYSBI with IR-cysteamine in 43 patients with cystinosis
- The pink dotted line shows intracellular cystine levels remaining controlled through a single 12 h PROCYSBI dose
- The twice-daily dosing of PROCYSBI enables patients to avoid night-time dosing

- 2 year treatment: preserved kidney function and improved quality of life (social function, school function, and total function scores)[2]

IR = immediate-release; RCT = randomised controlled trial.

1. Langman CB, et al. Clin J Am Soc Nephrol 2012;7:1112–1120 [Erratum in Clin J Am Soc Nephrol. 2013;8:468]; 2. Langman CB, et al. J Pediatr 2014;165:528-33.e1

What is the advice around food and drink with PROCYSBI?

PROCYSBI administration

- PROCYSBI should be taken orally, either as a whole capsule or the capsule can be opened and the contents (microgranules) sprinkled into (acidic) food or drink[1]



- PRCYSBI sprinkled onto apple sauce can be given via a gastrostomy feeding tube (14 French or larger)[1]
- PROCYSBI should **not** be administered with food rich in fat or proteins, or with frozen food like ice cream[1]
- Food and drink with pH <5.5 (acid) shown not to compromise the integrity of PROCYSBI beads in an *in vitro* study[2]

With or without food?

- Ideally, patients should try to avoid meals for at least 1 hour before and 1 hour after taking PROCYSBI[1]
- If fasting is not possible, patients should eat a small amount (~100 g) of food (preferably carbohydrates) during the hour before and after PROCYSBI dose[1]

It is important to take PROCYSBI at the same times every day, and with the same types and amounts of food[1]

1. PROCYSBI EU Summary of Product Characteristics. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002465/WC500151313.pdf; **2.** Pavloff N et al. American Pharmacists Association Annual Meeting & Exposition, March 24–27, 2017, San Francisco, CA; poster.

Dutch & Flemish Patients' Reported Outcomes Study

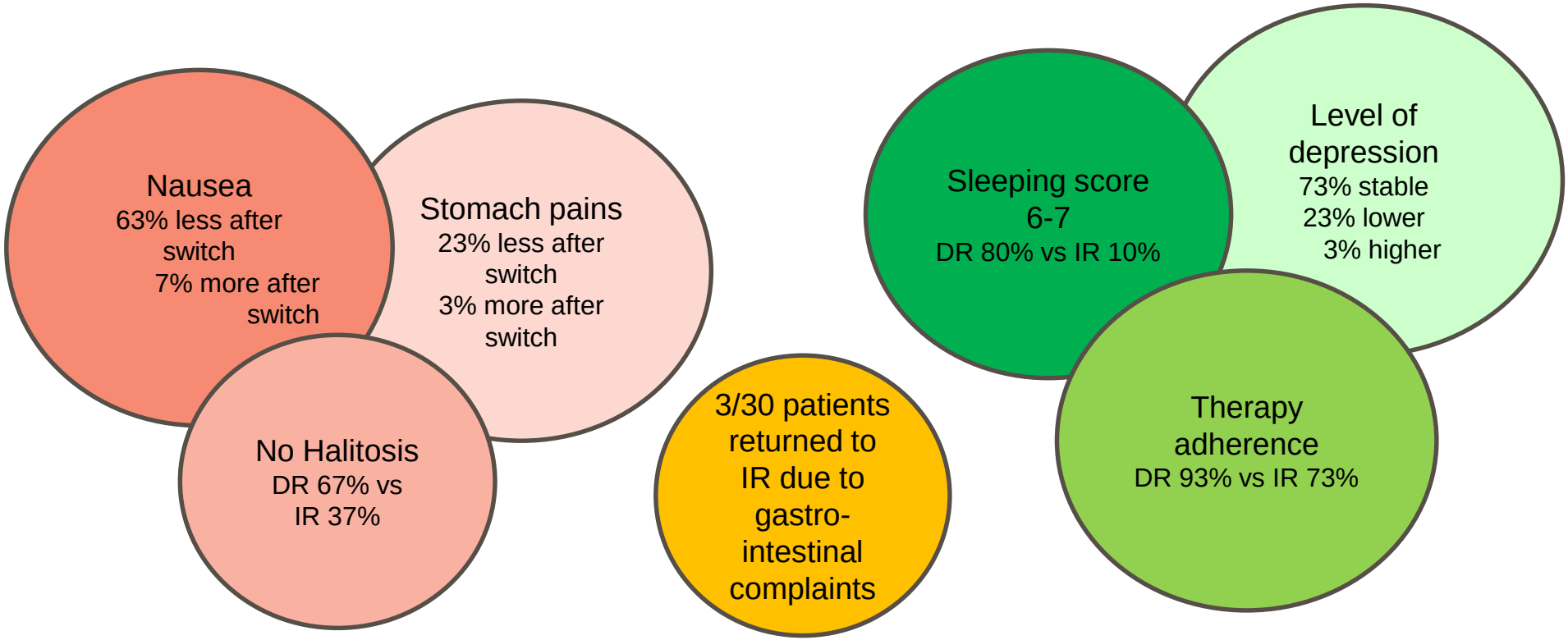
- Retrospective questionnaire study organized by patients' advocate organisation 'Cystinose groep Nederland en Vlaanderen'

- **Objective**: analysing burden of treatment, adherence to therapy and side effects after switch from IR to DR cysteamine

- n = 30 patients on average 2 years after the switch

de Vreugd et al. 2024 OC 60 SSIEM, JIMD 2024, 47, S1, p67

Self-Reported Outcomes



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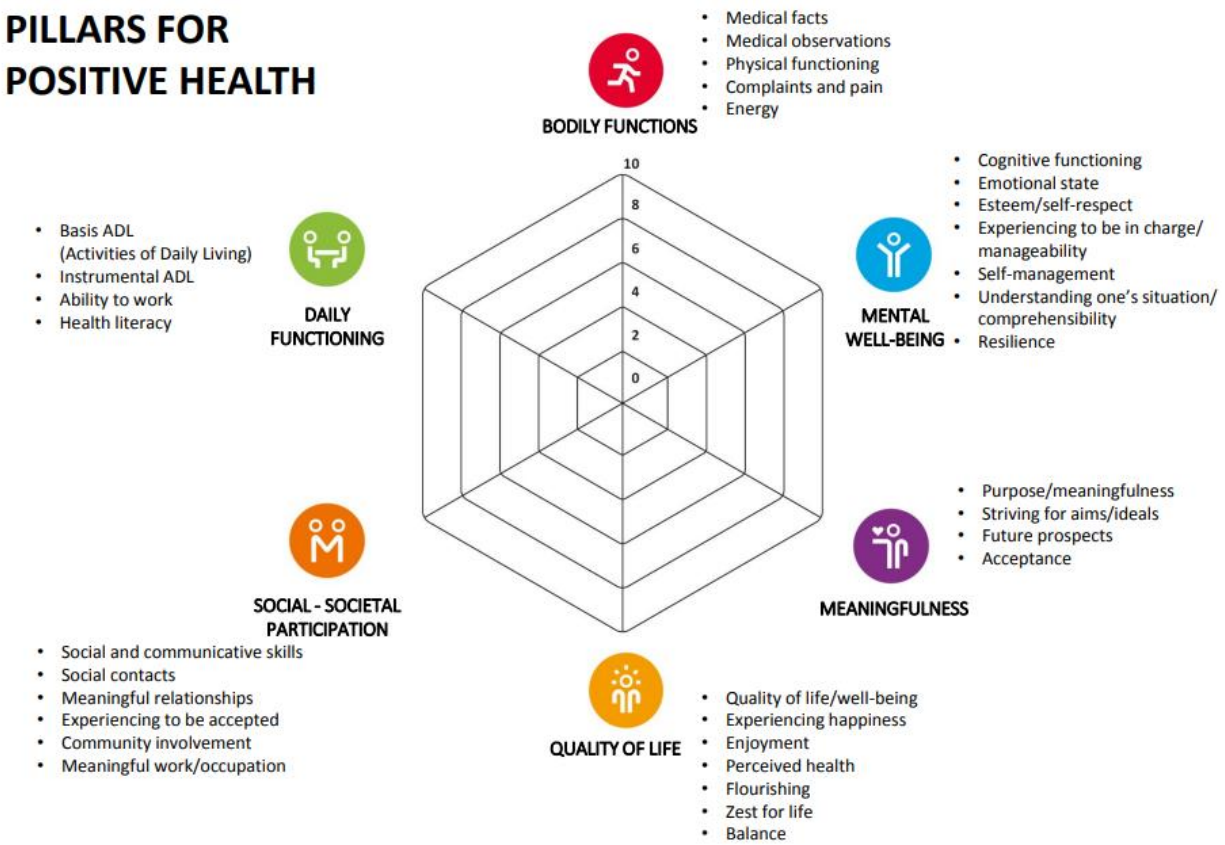
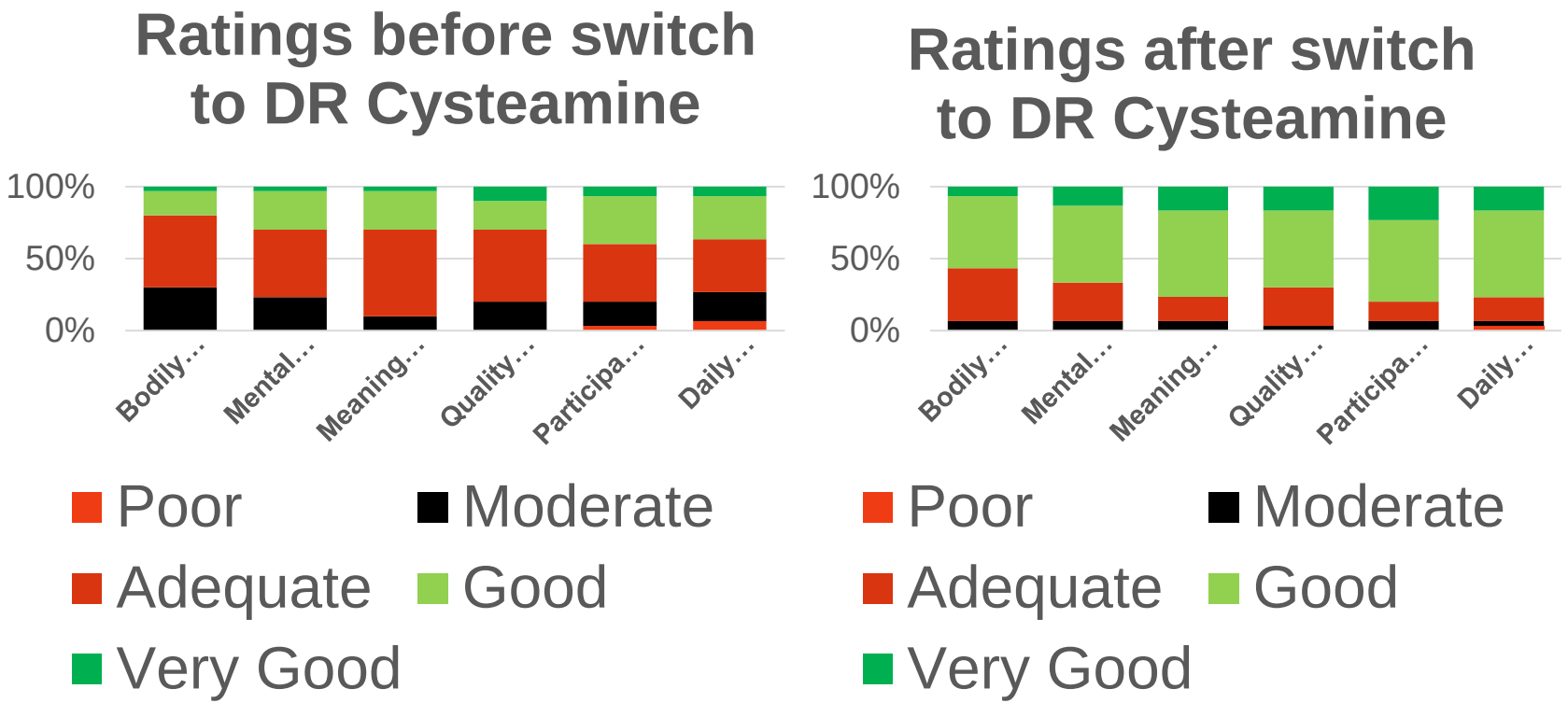
Positive Health Concept



Huber, M., van Vliet, M., Giezenberg, M., Winkens, B., Heerkens, Y., Dagnelie, P. C., & Knottnerus, J. A. (2016). Towards a 'patient-centred' operationalisation of the new dynamic concept of health: a mixed methods study. *BMJ Open*, *6*(1), e010091. https://doi.org/10.1136/bmjopen-2015-010091

Effect on Positive Health Dimensions



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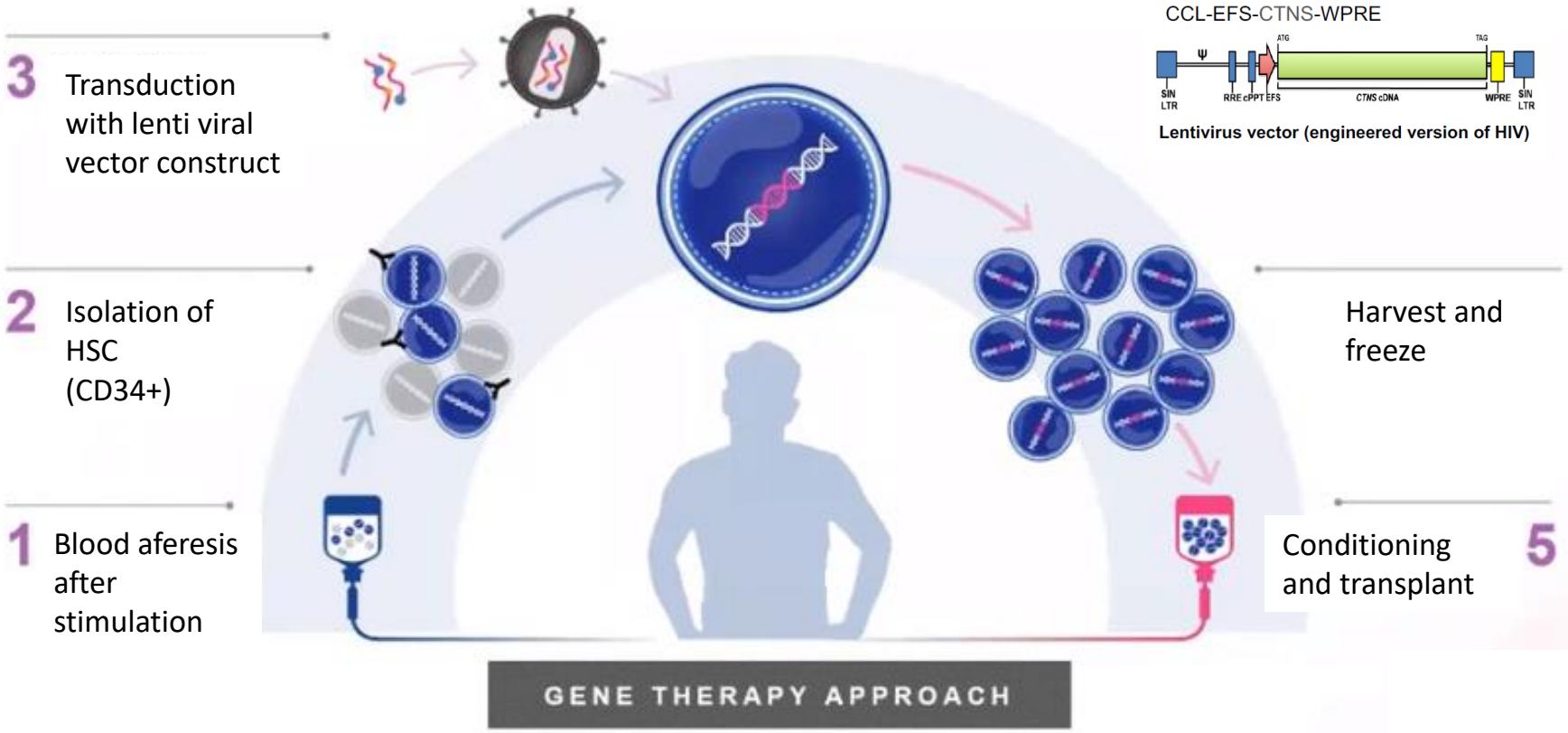
Gene therapy

Hematopoietic Stem Cell Gene Therapy for Cystinosis: a phase 1/2 clinical trial



Slide Courtesy prof. Stéphanie Cherqui University of California San Diego and AVROBIO

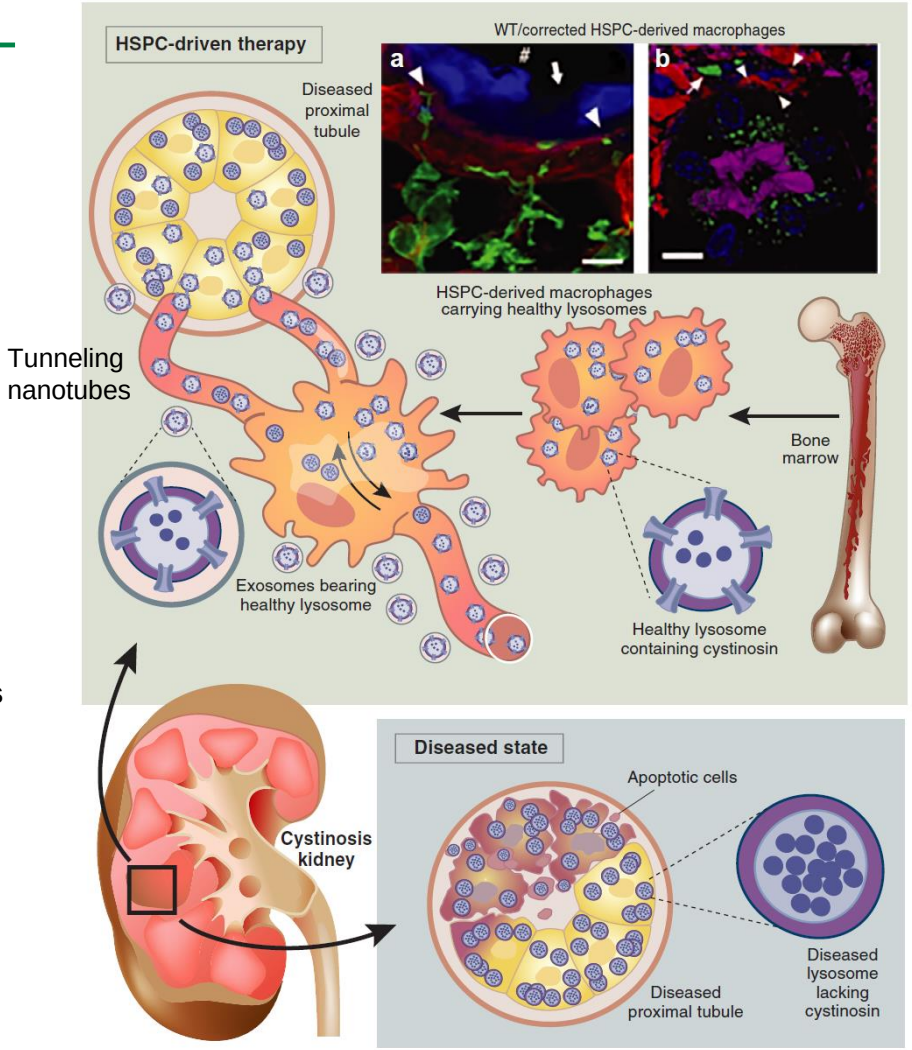
www.kidney-international.org

Targeted gene therapy for rare genetic kidney diseases

Veenita Khare[1] and Stephanie Cherqui[1]

[1]Department of Pediatrics, Division of Genetics, University of California, San Diego, La Jolla, California, USA

- Cystine accumulation => cell stress and subsequent apoptosis of proximal tubular cells (PTCs).
- Transplantation of ***CTNS*-expressing HSPCs** lead to their **differentiation** in **macrophages in the kidney interstitium** surrounding the proximal tubules.
- HSPC-derived macrophages generate multiple **tubular protrusions (tunneling nanotubes (TNTs))** that can extend across the **tubular basement membrane** (TBM) of PTCs, facilitating the bidirectional **transfer of lysosomes**.
- Extracellular exosomes may serve as another mechanism for transferring cystinosin to injured kidney cells



Kidney Int 2024

Hematopoietic Stem Cell Gene Therapy for Cystinosis: a phase 1/2 clinical trial: results

- 6 adult cystinosis patients with kidney failure transplanted, 4 with kidney graft

✓ No unexpected adverse effects

✓ Low cystine levels in white blood cells

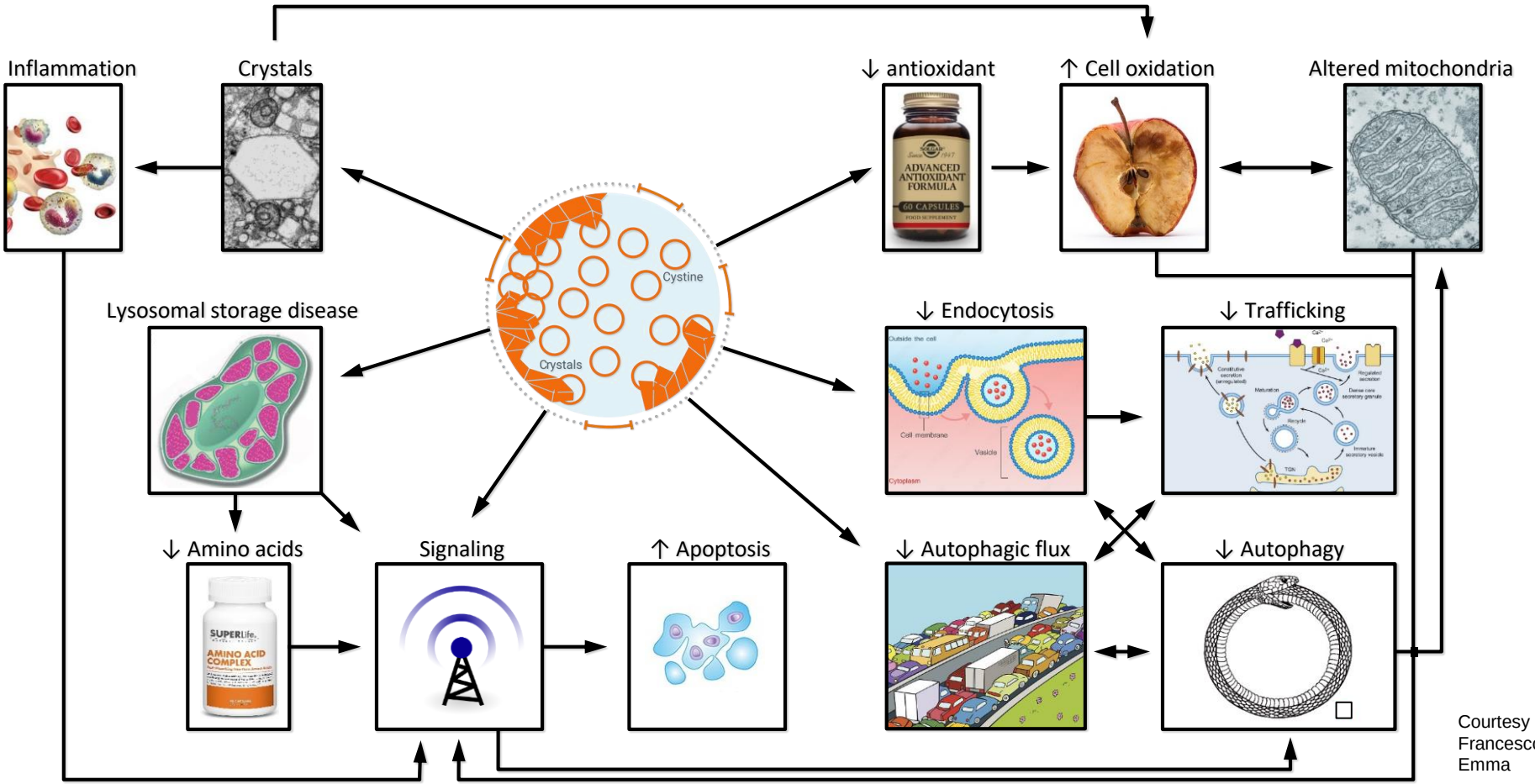
✓ Reduction of cystine crystals in the tissues

✓ Restauration of melatonin synthesis in the hair

- Long-term follow-up evaluation is ongoing
- Clinical trials in children prior to kidney failure are planed
- Prevention of myopathy and CNS complications?

Slide Courtesy of Prof. Stéphanie Cherqui University of California San Diego

Mechanisms of cell damage in nephropathic cystinosis => future approaches?



Ketogenic diet

Editorial

Let Food Be Thy Medicine

Potential of Dietary Management in Cystinosis

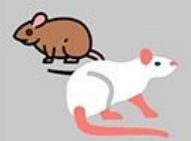
Elena Levtchenko [1] and Fanny Oliveira Arcolino[1,2]

JASN 35: 1456–1459, 2024. doi: https:/ / doi.org/ 10.1681/ ASN.0000000509

"Let food be thy medicine" is a quote attributed to Hippocrates (400BC), who recognized fasting as the only effective therapy against epilepsy, suggesting that dietary interventions hold potential for treating human diseases. In 1921, Russel Wilder was the first to propose that a ketone-generating diet could be as effective as fasting for treating epilepsy, and he coined the term "ketogenic diet." [1]

Ketogenic Diet and Progression of Kidney Disease in Animal Models of Nephropathic Cystinosis

JASN
Journal of the American Society of Nephrology



Ctns $^{-/-}$ rodents (mice and rats)

Fed ketogenic diets at specific timeframes

Followed for Fanconi syndrome
Polyuria
Low molecular weight proteinuria
Glycosuria

Ctns $^{-/-}$ mice fed with ketogenic diet from 3 to 12 months of age

Nearly complete prevention of Fanconi syndrome

12-month BUN was higher in standard diet cystinotic vs wild-type mice, but not in mice on a ketogenic diet

Benefits were also seen in mice with proximal tubular dysfunction if they were fed a ketogenic diet at age 6 to15 months

Microscopic Improvements:

Reduction of interstitial cell infiltration (CD3 and CD68 positive cells)
Reduction of interstitial fibrosis
Reduction of apoptosis (cleaved caspase 3 levels)
Indirect evidence of restoration of a normal autophagic flux (SQSTM1/p62 and LC3-II expression)

Although slightly less pronounced, these results were replicated in Ctns $^{-/-}$ rats fed with ketogenic diet from 2 to 8 months of life

Conclusions: These results indicate significant mitigation of the kidney phenotype in cystinotic animals fed with ketogenic diets.

Francesco Bellomo, Sara Pugliese, Sara Cairoli, et al. ***Ketogenic Diet and Progression of Kidney Disease in Animal Models of Nephropathic Cystinosis***. JASN 2024 Nov 1;35(11):1493-1506

Editorial

Let Food Be Thy Medicine

Potential of Dietary Management in Cystinosis

Elena Levtchenko [1] and Fanny Oliveira Arcolino [1,2]

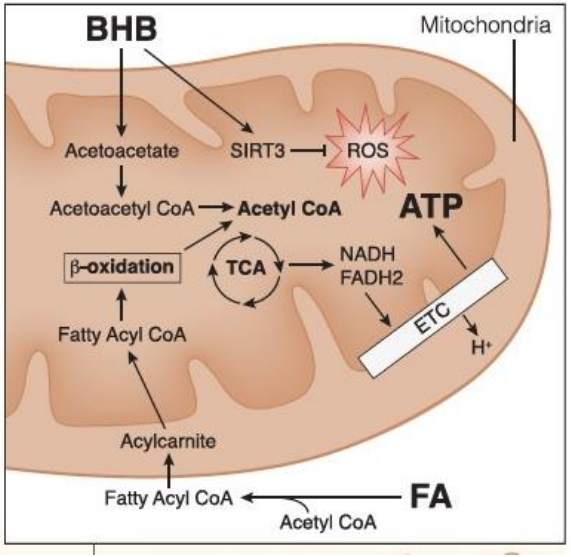
- ✓ ß-hydroxybutyrate (BHB)
- ✓ Faty acid (FA)

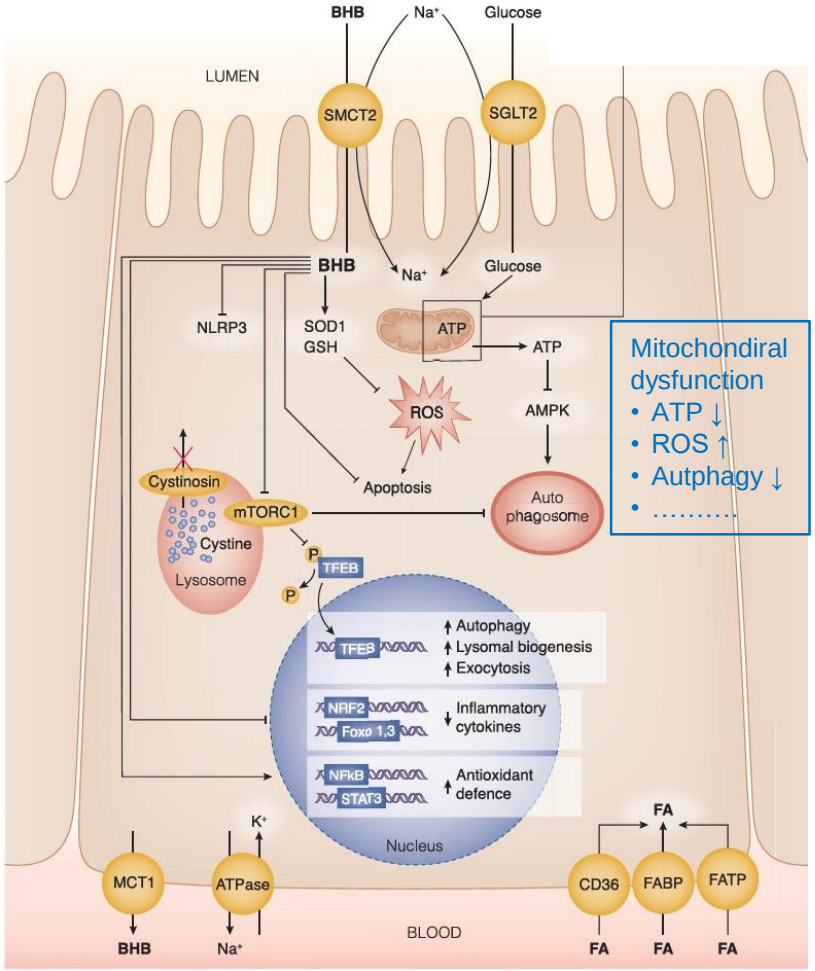
⇒ Acetyl CoA ↑, Krebs cycle ↑

⇒ mitochondrial

- ATP production ↑
- Oxidative metabolism ↑
- Autophagy ↑
- Exocytosis ↑
- Inflammatory cytokines ↓

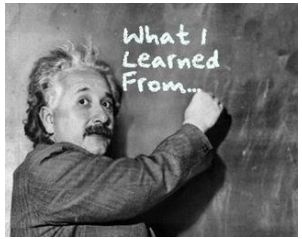
=> Kidney damage ↓





Mitochondiral dysfunction
- ATP ↓
- ROS ↑
- Autphagy ↓
- ……

JASN 2024 Nov 1;35(11):1456-1459



How to improve long-term outcome in patients with cystinosis?

– Early (neonatal) diagnosis and immediate start of cysteamine treatment

– Multi-disciplinary care: nutrition, psychosocial aspects, adherence support.

– Switch to DR cysteamine is associated with overall positive experience, better quality of life, and better adherence => better outcome

– Careful transition from pediatric to adult care

– New therapies are under way, but their efficiency still need to be proven

Thank you for your attention!

Medizinische Hochschule Hannover