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Advanced Webinars on Rare Kidney Disorders

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Rare Kidney Disease
Reference Network

Date: 28 April 2020

Topic: Cystinuria

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Moderator:

Cystinuria

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ERKNet Webinar

28-04-2020

Plan

- Epidemiology
- Genetics
- Pathophysiology
- Diagnosis
- Long term Outcomes
- Treatment
  - Urological
  - Medical
  - Follow up

Epidemiology

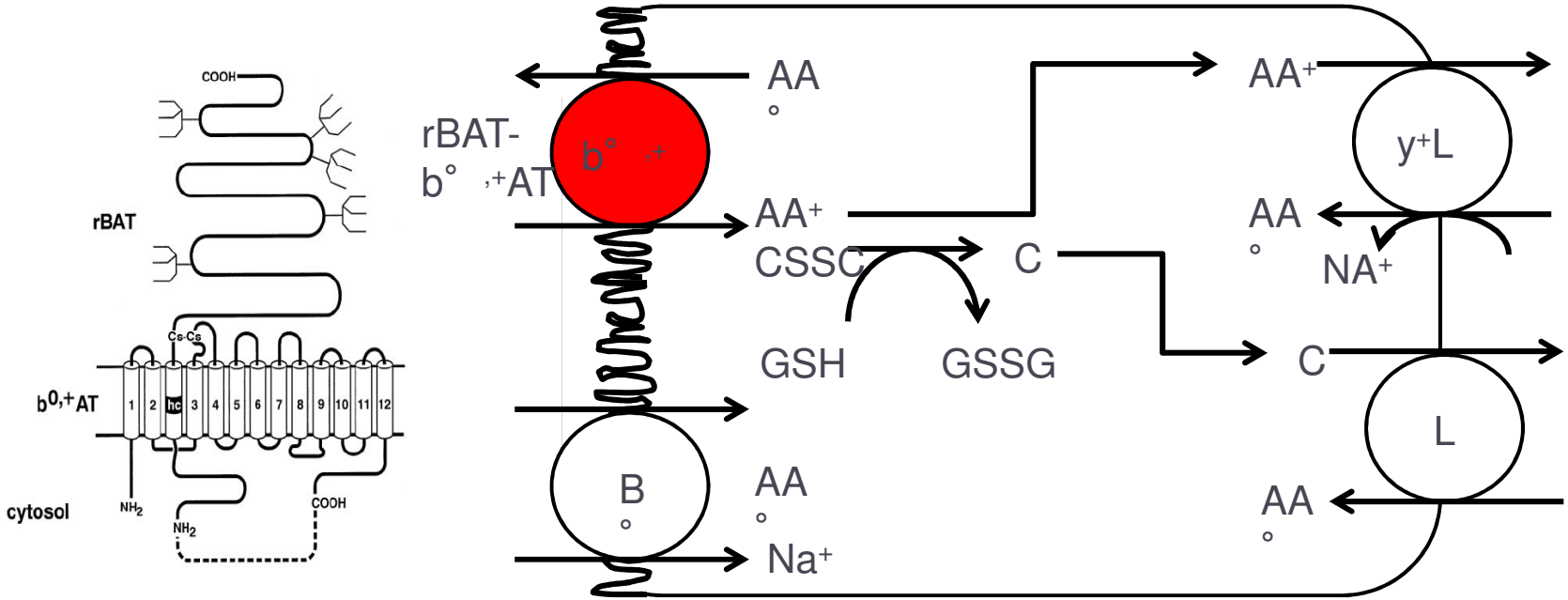
- 1 % of Adult stones
- 8 -10 % of children stones
- The most prevalent hereditary stone disease
- Prevalence # 1/7000
  - Prevalence higher in some populations with high consangunity (1/2500 lebanon jews)

Andreassen KH, Urolithiasis 2016

Physiopathology

Lack of reabsorption in the Proximal tubule of

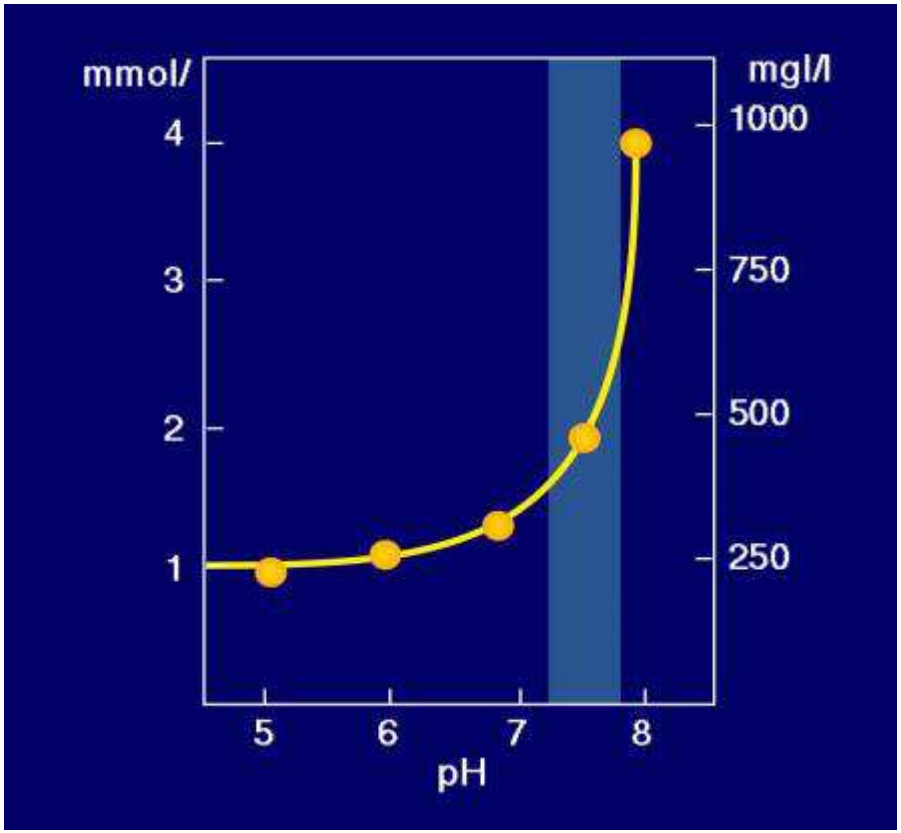
- **cystine**
- and dibasics AA (arginine, lysine, ornithine)
- also in the gut



Pfeiffer R, Mol Biol Cell, 1999; Bröer S, Physiol Rev, 2008

Physiopathology

- **Low solubility of cystine at urinary pH <7**



≈ 1 mmol/l (250 mg/l) at pH < 7
2 mmol/l (500 mg/l) at pH 7.5

cystine output:

Homozygotes

= 2.5 to 6 mmol/d

(600 to 1400 mg/d)

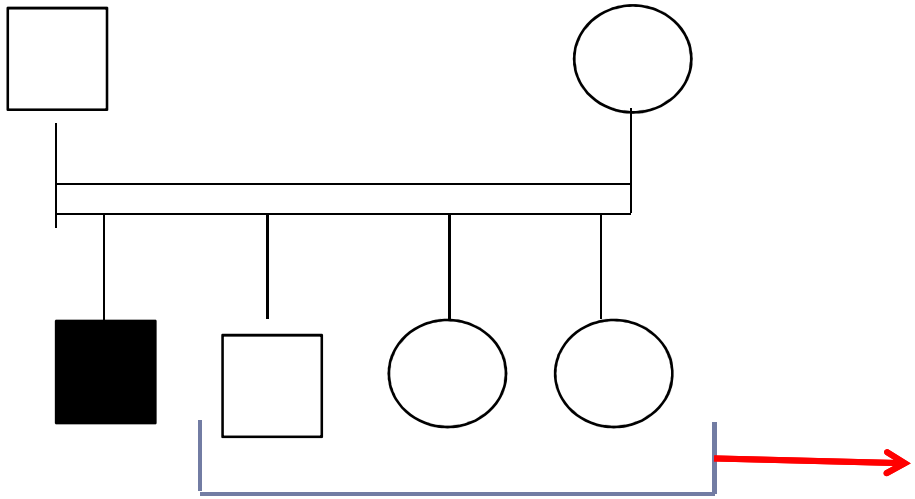
Normal < 0.20 mmol/d (50 mg/d)

Urinary stones
=
Only clinical consequence

Genetics

- Autosomal recessive
- Increased risk by consanguinity
- 25% of offsprings affected (both sex equally)
- Parents usually do NOT develop cystine stones

Don't forget 5-8% of the general population develop stones
Unrelated to cystinuria (CaOx, CaPho, etc)



Screen
at risk siblings +++

Classification based on Genetics

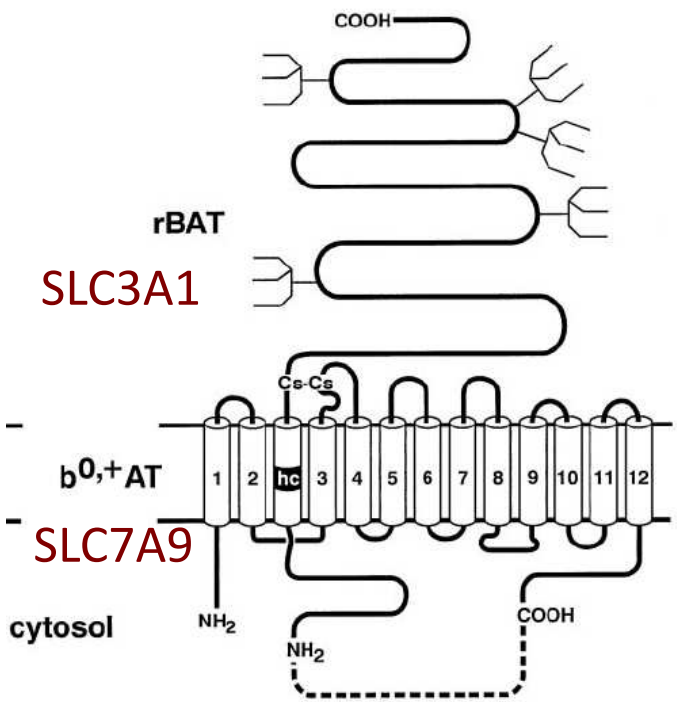


Figure 2.

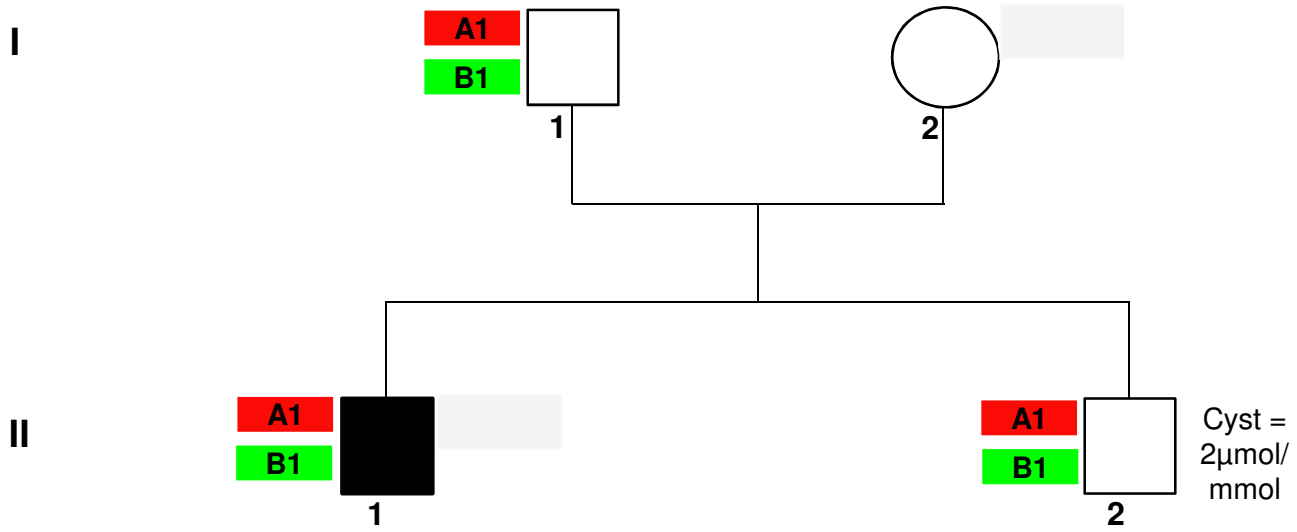
- **Type A (AA)** - SLC3A1$^{mut/mut}$
  - Heterozygotes SLC3A1$^{mut/+}$:
    - Normal Cystinuria
    - Exceptionally cystinuria ↗: Dup E5-E9
- **Type B (BB)** - SLC7A9$^{mut/mut}$
  - Heterozygotes SLC7A9$^{mut/+}$:
    - 86% ↗cystinuria (≈ 700 µmol/j)
    - 14% cystinuria normal
- **Digenic Type AB (?)**

  SLC3A1$^{mut/+}$ et SLC7A9$^{mut/+}$

Gaildrat P, Molecular Genetics & Genomic Medicine, 2017

Font-Llijos M, J Med Genet, 2005
Dello Strogolo L, J Am Soc Nephrol. 2002

MLPA detection of large rearrangement in SLC3A1
Reclassify a suspected AB genotype to AAB



A1 c. 163C>T

B1 c. 544G>A

AAB SLC3A1$^{mut/mut}$ SLC7A9$^{mut/+}$

or BBA SLC7A9$^{mut/mut}$ and SLC3A1$^{mut/+}$

Gaildrat P, Molecular Genetics & Genomic Medicine, 2017

Urinary dibasic AA excretion according to Genotype in heterozygotes

Type A= SLC3A1 Type B= SLC7A9

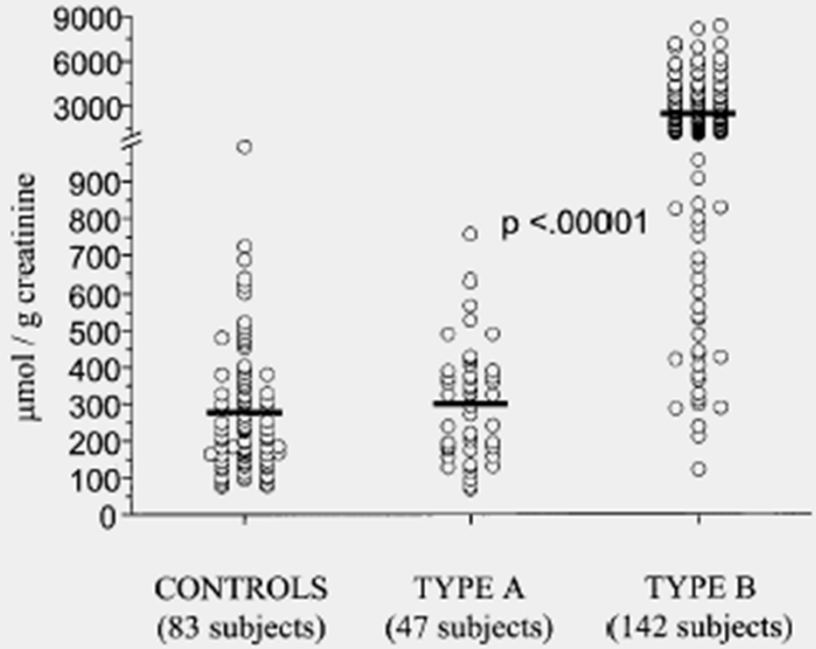


Figure 4. Sum of cystine, lysine, ornithine, arginine in parents of probands (obligated heterozygotes), with a precise genetic characterization and in controls (relatives of the affected, without the mutation of the probands).

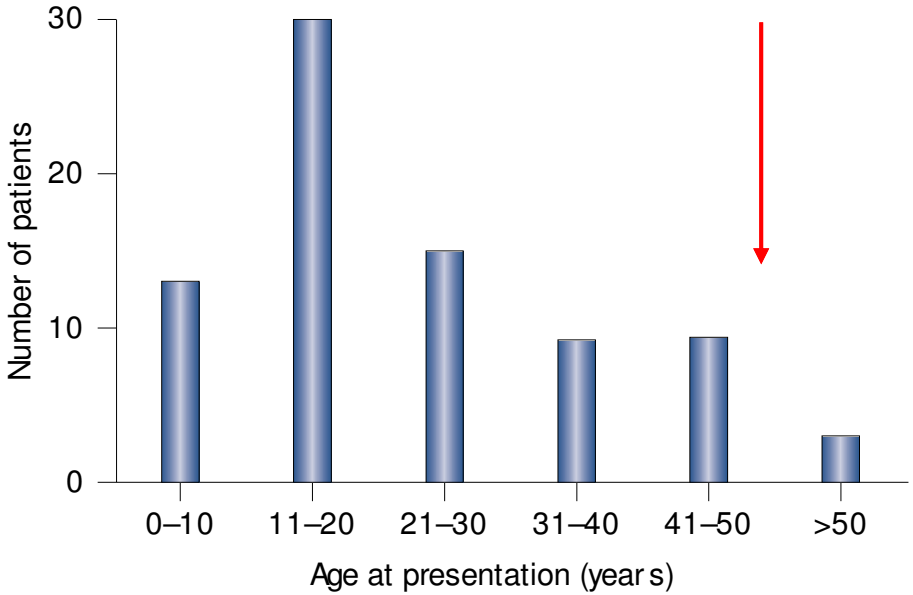
Sum Cys+Lys+Orn+Arg

Dello Strologo et al, JASN, 2002, 13: 2547

MCQ 1

Diagnosis

- Family History
- Median age at first symptoms # 16 years
- Can be much later !



Andreassen KH, Urolithiasis, 2016
Rhodes HL, Clin J Am Soc Nephrol, 2015
Prot-Bertoye C, Clin J Am Soc Nephrol, 2015
Thomas K, Nat Rev Urol, 2014

An uncommon early Diagnosis

- Prenatal hyperechogenic colon

  - After 22 wks of pregnancy

    Amniotic fluid produced by diseased kidneys lead to accumulation and precipitation of colic cystine

  - Genotype/Phenotype Correlation ?
    - Mutation SLC3A1 (80%) *vs 49%*
    - « severe » Mutation (45%) *vs 28%*

Amat S, Ultrasound Obstet Gynecol, 2011; Tostivint T, Clin Genet, 2017

Radiology

KUB X Ray

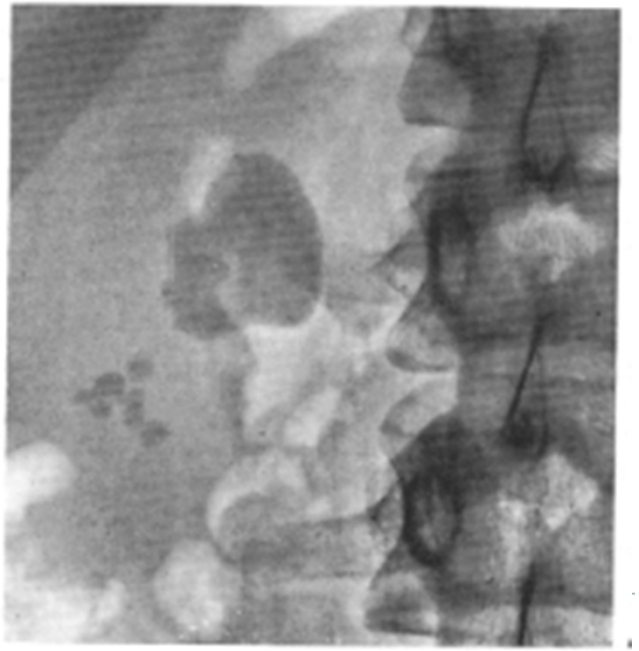
Small stones can be translucent

opacity < vertebral bones

often multiples and bilateral

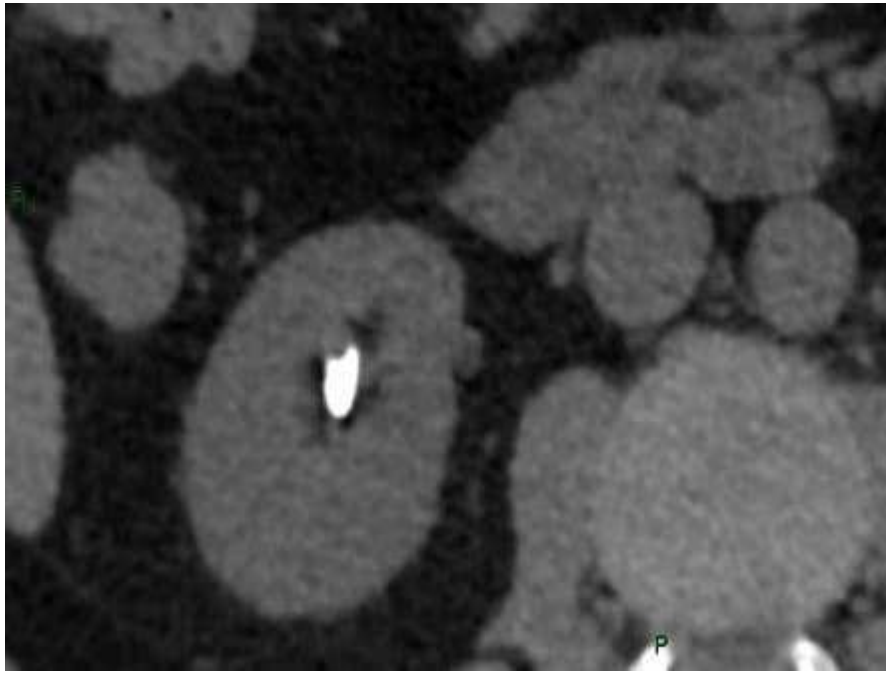
Smooth aspect

Often staghorn calculi



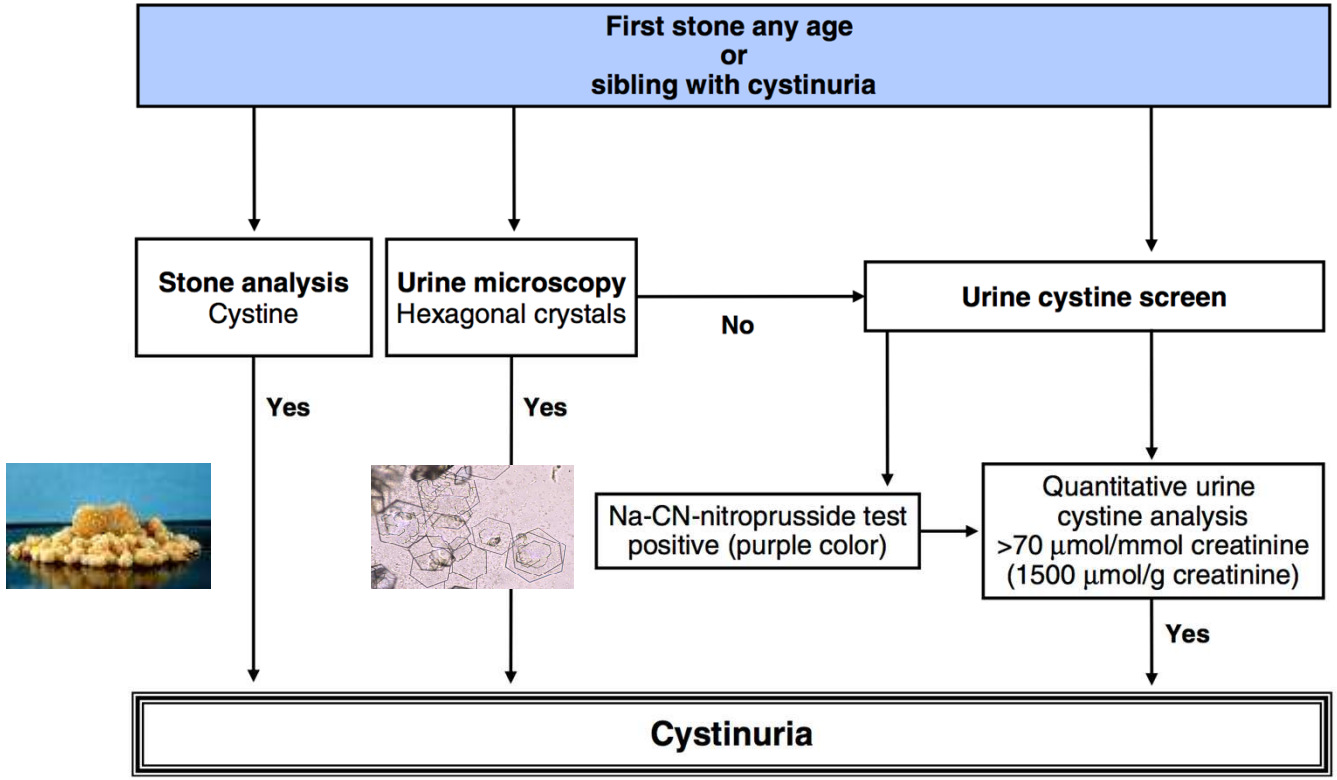
Low dose CT KUB

600-700 HU

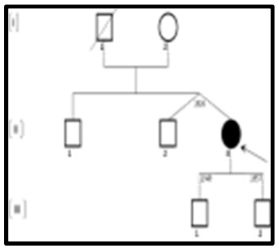


MCQ 2

Diagnosis of Cystinuria



Family History often lacking



Autosomal Recessive

Edvardsson et al, Pediatr Nephrol, 2013,

Stone activity is much higher than in classical CaOx stones

- Up to 0,15 to 0,35 /patient/year

-Infectious obstructive complications

-Risk of repetitive interventions
(hemorrhage, infections, ureteral stenosis)

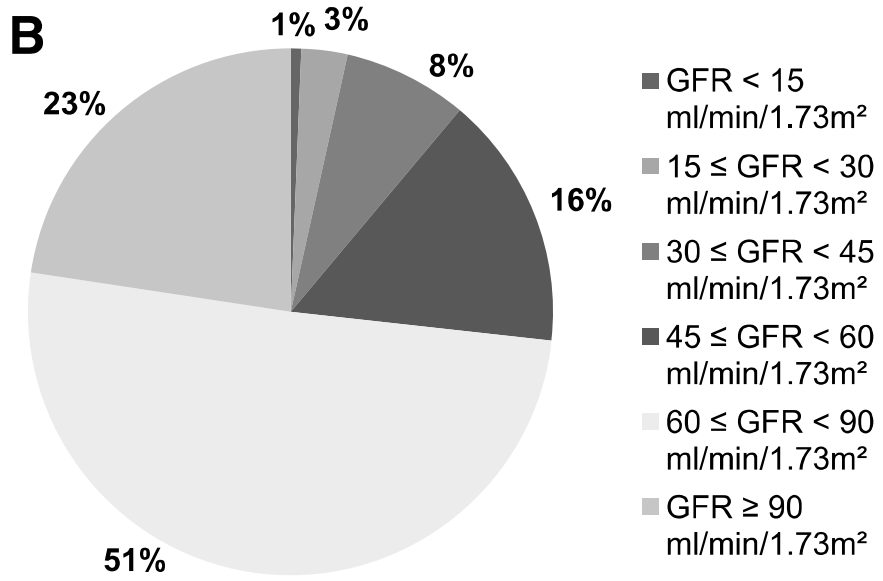
-Quality of life is affected
Psychological
Socio-professionnal

Thomas K, Nat Rev Urol, 2014; Dello Strologo et al, JASN, 2002; Modersitski, Urolithiasis 2019

CKD and Its Risk Factors among Patients with Cystinuria

Caroline Prot-Bertoye, Saïd Lebbah, Michel Daudon, Isabelle Tostivint, Pierre Bataille, Franck Bridoux, Pierre Brignon, Christian Choquenet, Pierre Cochat, Christian Combe, Pierre Conort, Stéphane Decramer, Bertrand Doré, Bertrand Dussol, Marie Essig, Nicolas Gaunez, Dominique Joly, Sophie Le Toquin-Bernard, Arnaud Méjean, Paul Meria, Denis Morin, Hung Viet N'Guyen, Christian Noël, Michel Normand, Michel Pietak, Pierre Ronco, Christian Saussine, Michel Tsimaratos, Gérard Friedlander, Olivier Traxer, Bertrand Knebelmann, and Marie Courbebaisse on behalf of the French Cystinuria Group

- 314 patients >16 years (median age = 38.7 yrs [16.2–86.6])
- 27% have CKD3 or less (eGFR< 60 ml/min/1.73m$^{2)}$



Prot-Bertoye C, Clin J Am Soc Nephrol, 2015

Factors associated with CKD

- Age (OR=1.05 [1.03–1.07], *P*<0.001)
- HBP (OR=3.30 [1.54-7.10], *P*=0.002)

  29% of patients had HBP

- Nephron Reduction (OR=4.39 [2.00-9.62], *P*<0.001)
  - ✓ Partial or total nephrectomy
  - ✓ Single congenital kidney
  - ✓ ≥1 kidney length < 10 cm

50 % (N= 117) of patients > 16 yrs had severe kidney reduction:
82 kidneys <10 cm
34 partial/total nephrectomy
1 congenital solitary kidney

PCNL: 45 % of patients

Prot-Bertoye C, Clin J Am Soc Nephrol, 2015

Urological Treatment

- Cystinuria: lead to more interventions than other stones
  - 0.06 – 0.5 ±0.7 interventions/patient/yr
- Cystinuria = risk factor for nephrectomy
  - 7.7% – 20 % of patients

- Cystine stones relatively resistant to ESWL
- Urological intervention as soon as a stone is >5mm ?
- Cystinuria patients often undergo frequent procedures, therefore, ureteral stones and renal stones <20 mm should be treated with flexible ureteroscopy to avoid the insult of percutaneous nephrolithotomy.
- Stent dwell time should be minimized due to risk of rapid encrustation.

Chow GK, J Urol, 1996 *Thomas K, Nat Rev Urol, 2014* *Trinchieri A, Urol res, 2007* *Assimos, DG, J urol, 2002* *Lindell A, Nephron, 1997*
Barbey F, J Urol 2000 *Andreassen KH, Urolithiasis 2016* *Kirsch-Noir F, Progr Urol, 2000* *Lindell A, Urol Res, 1995* *Worcester EM, J urol, 2006*

MCQ 3

Medical Treatment : Diet I

- ↘ **Methionin rich food (= precursor of cystine)**
  - essentiel AA (needs 1200-1400 mg/j)
  - **Eggs** (500mg/100g), **gruyère /parmesan** (900mg/100g) Meat (500-700 mg/g)
  - Limit animal protein intake 120-150 g /j ; # 0,8g/Kg/dy in adults
  - ↘ cystinuria 0,5 à 1 mmol/d
  - Decreases acid load

- ↘ **NaCl intake**

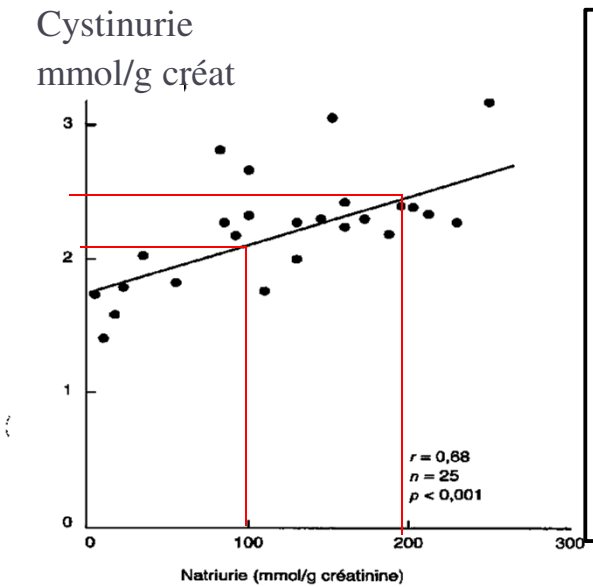


Figure 4. Relation entre la natriurèse et la cystinurie.

→From 200 mmol/d of Na(12g Nacl) to 100 mmol Na/d (6g NaCl)
→↘cystinuria by 0,5 mmol/j

→Advise NaCl < 6g/dy

→1-1.5 mEq Na /Kg/dy for children

Medical Treatment: Diet II

Diuresis > 3 l/24h in adults

2l/1.73 m2 in Children

0022-5347/00/1635-1419/0
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MEDICAL TREATMENT OF CYSTINURIA: CRITICAL REAPPRAISAL OF LONG-TERM RESULTS

FRÉDÉRIC BARBEY,* DOMINIQUE JOLY, PHILIPPE RIEU, ARNAUD MÉJEAN, MICHEL DAUDON AND PAUL JUNGERS

From the Departments of Nephrology, Urology and Biochemistry and INSERM U507, Necker Hospital, Paris, France

TABLE 3. *Characteristics of patients with long-term therapy success versus failure*

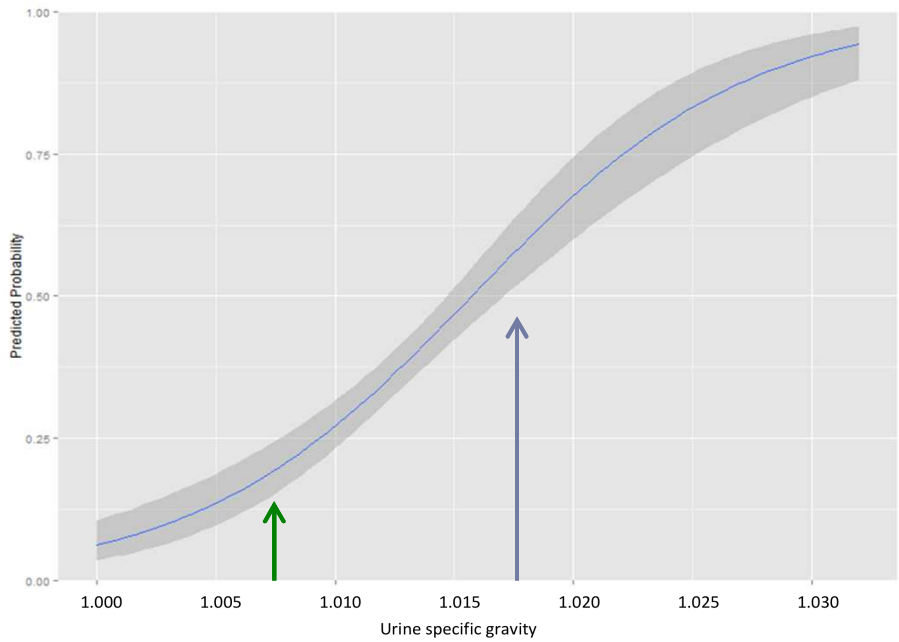
	Success	Failure	p Value
No. pts.	15	12	
Mean age ± SD:			
At initial stone episode	18.5 ± 8.7	21.0 ± 10.4	Not significant
At referral	31.0 ± 9.8	29.1 ± 12.1	Not significant
Pre-referral period			
No. pt.-yrs.	177	97	Not significant
Mean yrs. ± SD	11.8 ± 9.6	8.1 ± 6.8	Not significant
No. stone episodes/pt.-yr.	0.74	1.28	Not significant
No. urological procedures/pt.-yr.	0.30	0.29	Not significant
Mean cystine excretion ± SD (mg./24 hrs.)	863 ± 253	761 ± 270	Not significant
Mean serum creatinine ± SD (μmol./l.)	92 ± 16	88 ± 14	Not significant
Mean creatinine clearance ± SD (ml./min./1.73 m.^{2})	79 ± 11	79 ± 12	Not significant
Therapeutic period			
No. pt.-yrs.	145	167	Not significant
Mean yrs. ± SD	9.6 ± 8.6	13.9 ± 7.3	Not significant
Mean cystine excretion ± SD (mg./24 hrs.)	785 ± 282	669 ± 271	Not significant
Mean urine cystine concentration ± SD (mg./l.)	256 ± 102	291 ± 158	Not significant
No. pts. receiving thiols	4	5	Not significant
Mean urine vol. ± SD (ml./24 hrs.)	3,151 ± 587	2,446 ± 654	<0.006
Mean urine pH ± SD	7.6 ± 0.6	7.5 ± 0.5	Not significant
Mean serum creatinine ± SD (μmol./l.)	94 ± 21	95 ± 17	Not significant
Mean creatinine clearance ± SD (ml./min./1.73 m.^{2})	77 ± 12	70 ± 20	Not significant
No. stone episodes/pt.-yr.	0.076	0.33	<0.0001
No. urological procedures/pt.-yr.	0.006	0.26	<0.0001
No. pts. compliant with high fluid intake	11	4	Not significant

& Advise high water intake
-at bedtime
-upon awakening

& Increase water intake
if extrarenal loss
(fever, sports, diarrhea, etc)

Effect of Hyperdiuresis/ Low urine gravity on Cristalluria (a surrogate for stone recurrence)

- **Cristalluria in 89 patients**



Estimated predicted probability	0.06	0.14	0.27	0.47	0.68	0.83	0.92

& Aim 1:
U gravity ≤1.005
All day long including on first morning urine
Advise:
self monitoring of urine gravity (sticks) Or color chart

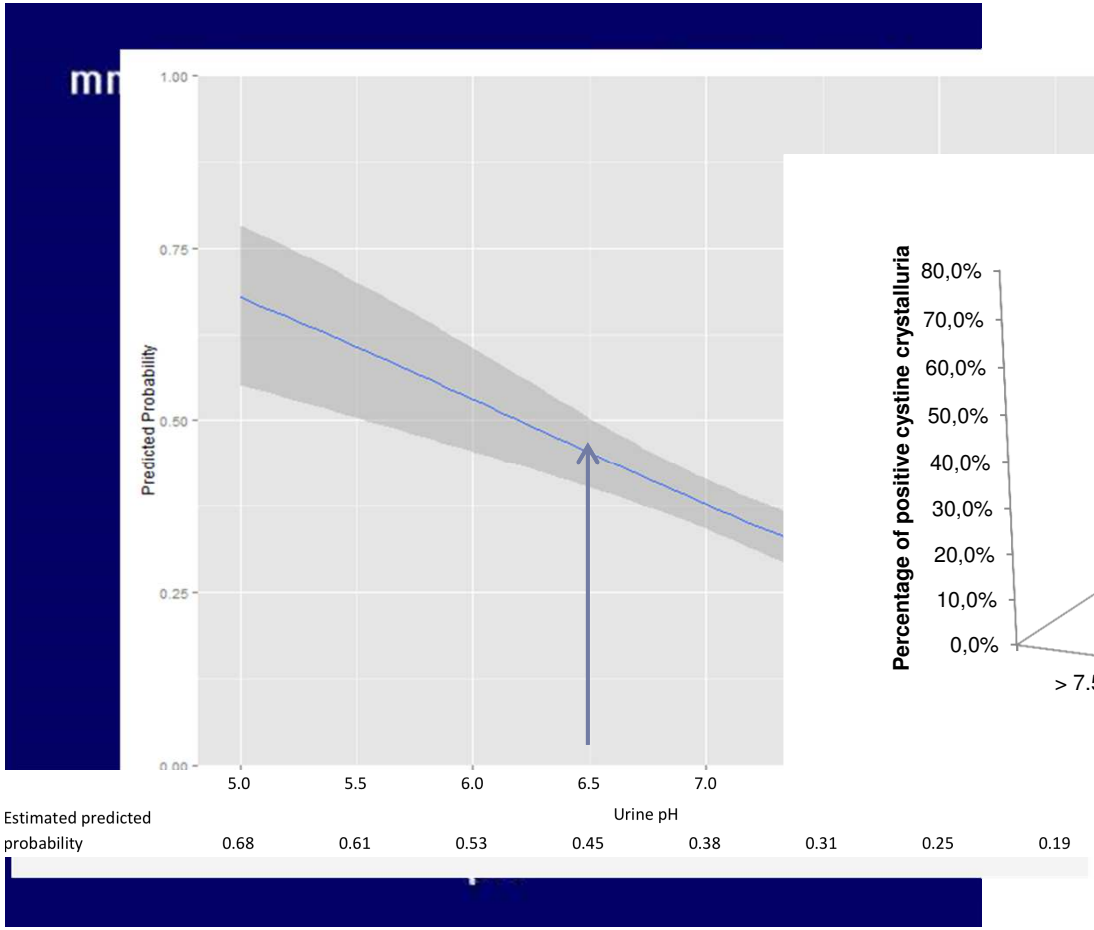
& Aim 2
Cystinuria < 1 mmol/l 24h urines AND morning sample

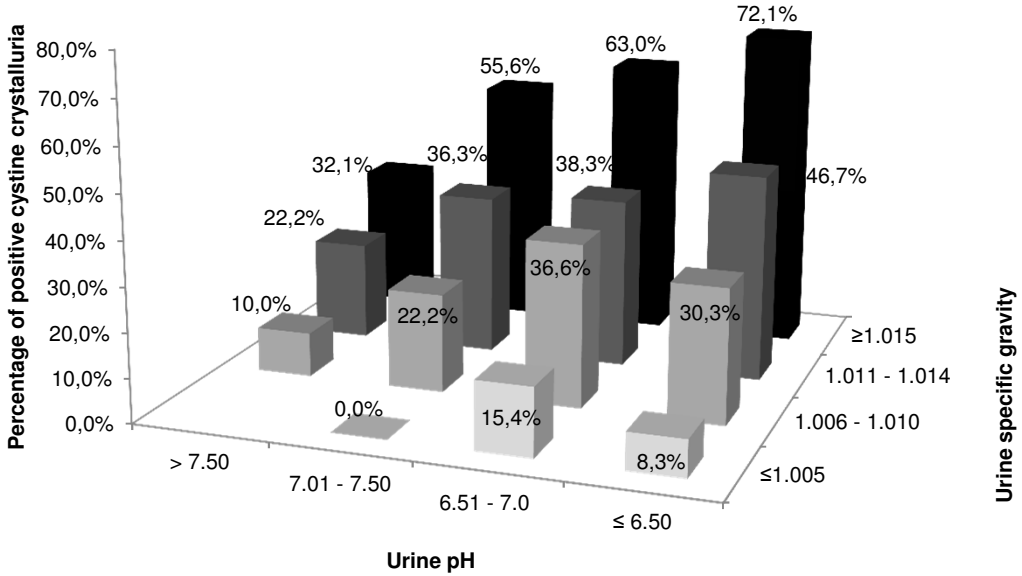
Prot-Bertoye C, BJU Int, 2019

MCQ 4

MCQ 5

Medical Treatment: Alcalinization





Prot-Bertoye C, soumis

Medical TRT: Alcalinization

- **Na Bicarbonate or K citrate ?**
- Same effect on U pH!

Urol Res (2001) 29:295–302
DOI 10.1007/s002400100200

ORIGINAL PAPER

Erik Fjellstedt · Torsten Denneberg
Jan-Olof Jeppsson · Hans-Göran Tiselius

A comparison of the effects of potassium citrate and sodium bicarbonate in the alkalinization of urine in homozygous cystinuria

U pH

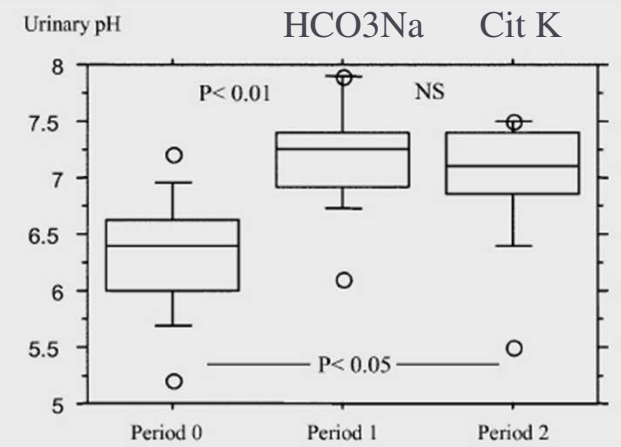


Fig. 2 Box plot of urinary pH during *Periods 0, 1 and 2* Box plot: *Lines* represent 10th–25th–50th–75th and 90th percentiles, respectively. *Circles* represent values below the 10th and above the 90th percentile

U Na

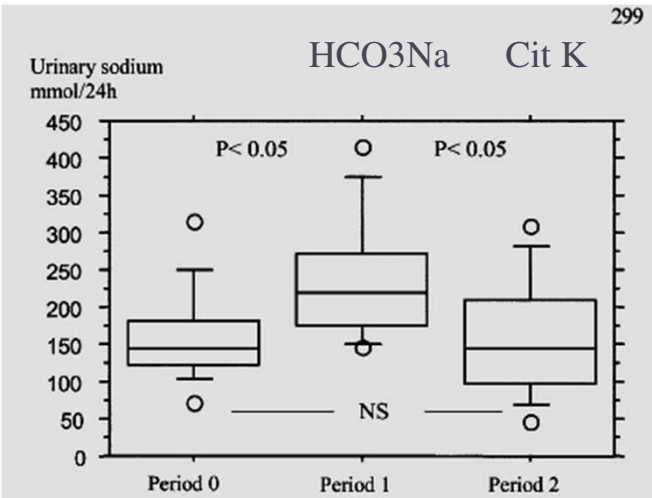


Fig. 3 Box plot of urinary sodium excretion. *NS* Not significant

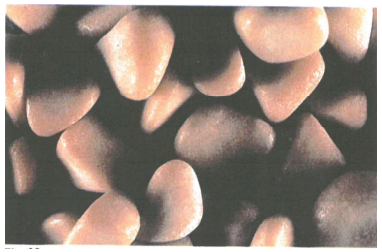
Medical TRT: Risk of Alcalinization?

- #Precipitation of Calcium Phosphate?

Parameters	OR (CI 95%)	*p*-value
pH		
pH ≤6.5	1	
6.5< pH ≤7.0	4.11 (2.02 – 8.39)	<0.001
7.0< pH ≤7.5	8.15 (3.74 – 17.74)	<0.001
7.5< pH ≤8.0	7.36 (3.22 – 16.82)	<0.001
pH > 8.0	6.09 (2.15 – 17.25)	<0.001
Specific gravity		
≤1.005	1	
1.006 – 1.010	1.35 (0.32 – 5.66)	0.68
1.011 – 1.014	1.91 (0.46 – 7.91)	0.37
≥1.015	2.51 (0.61 – 10.33)	0.20

OR: odds ratio, CI: confidence interval

15% of patients:
≥ 1 stone having
≥ 10% CaPho



Prot-Bertoye C, BJU Int 2019

Medical TRT: Alcalinization

- **Aim = pH U # 7,5 – 8**

Potassium Citrate

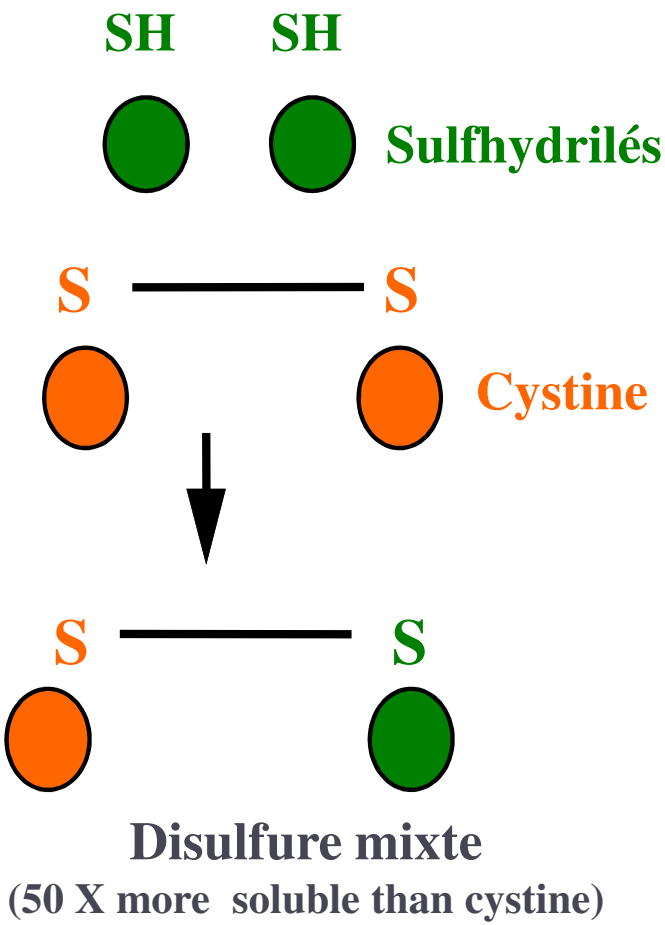
6 - 10 g/d (60-100 mEq/dy)
(children 60-80 mEq/1.73m2/d)
Pills in minimum 3 intakes/dy

or powder diluted in 2 l water

Na Bicarbonate
if digestive intolerance to K Citrate (10-30% of patients)

Medical Treatment

- Cystine chelators = Sulfhydryl drugs (= Cystin Binding Drugs (CBT)



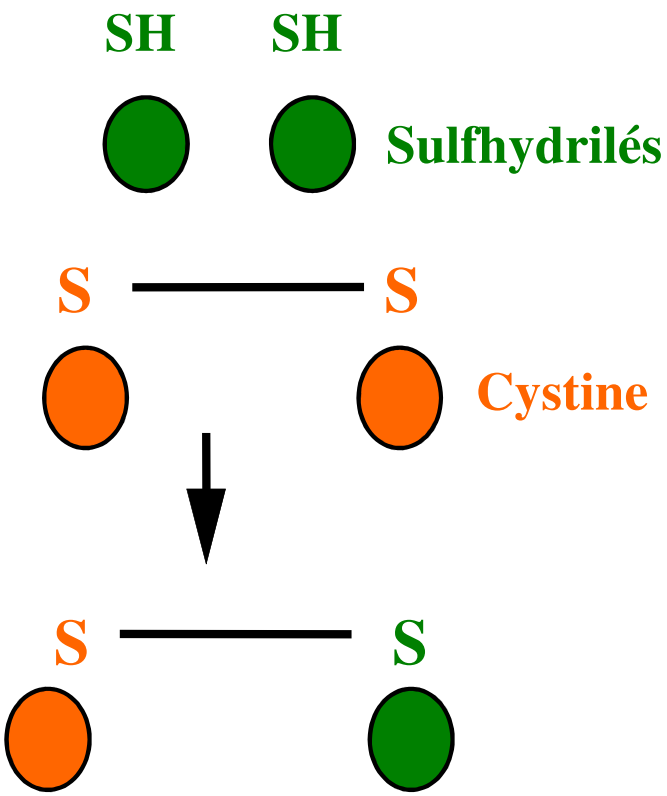
Only small studies
to show efficacy on clinical endpoints

Tiopronine
D-Penicillamine

Barbey, J Urol, 2000
Halperin EC, Yale J Biol Med, 1981
Lindell A, Urol Res, 1995
Chow, J Urol, 1996

Medical Treatment

- **CBD**



Disulfure mixte
(50 fois plus soluble que la cystine)

Risk of positive Cristalluria

Parameters	OR (CI 95%)	*p*-value
pH		
pH ≤6.5	1	
6.5< pH ≤7.0	0.77 (0.44 – 1.35)	0.35
7.0< pH ≤7.5	0.52 (0.28 – 0.95)	0.03
7.5< pH ≤8.0	0.26 (0.13 – 0.53)	<0.001
pH > 8.0	0.11 (0.04 – 0.31)	<0.001
Specific gravity		
≤1.005	1	
1.006 – 1.010	5.76 (1.45–22.85)	0.01
1.011 – 1.014	11.06 (2.76–44.26)	<0.001
≥1.015	26.93 (6.65–109.02)	<0.001
Cysteine-binding thiol (g/day)	0.63 (0.28 – 1.41)	0.26

OR: odds ratio, CI: confidence interval

Table 2.

Table 2. Multivariate analyses of associations between urine pH, urine specific gravity, and cysteine-binding thiol (D-penicillamine and/or tiopronin) with the risk that a given patient will have a cystine crystalluria. OR values were adjusted based on the delay between date of diagnosis and date of crystalluria measurement.

Prot-Bertoye C, BJU Int, 2019

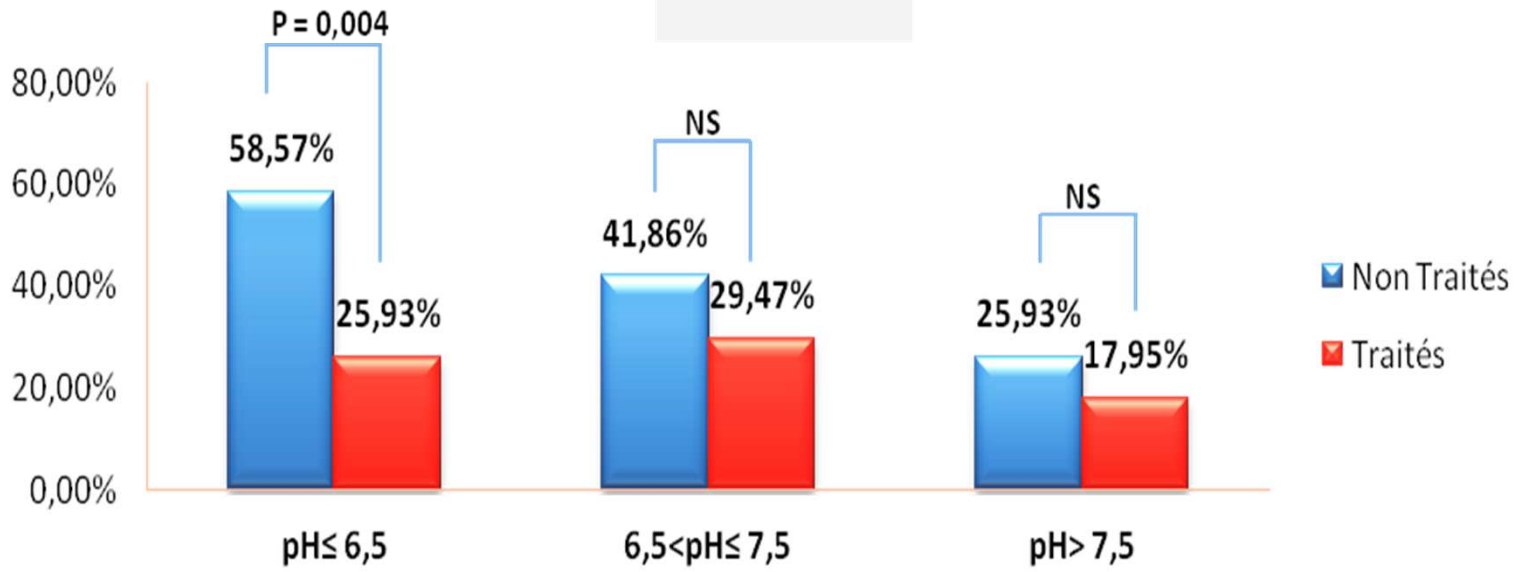
Medical Treatment

- **CBD:**
  - D-Pénicillamine (Trolovol®)
    - cp 300mg → 3 à 4 cp/d
  - Tiopronine (Acadione®/ Captimer/ Thiola (USA)
    - cp 250mg → 3 à 6 cp/d
  - Lopril (Captopril®)
    - No efficacy!

Progressive dosage (2cp/d to start)
Half at bedtime

Jungers P, Prog Urol, 2001
Joly D, Pediatr Nephrol, 1999

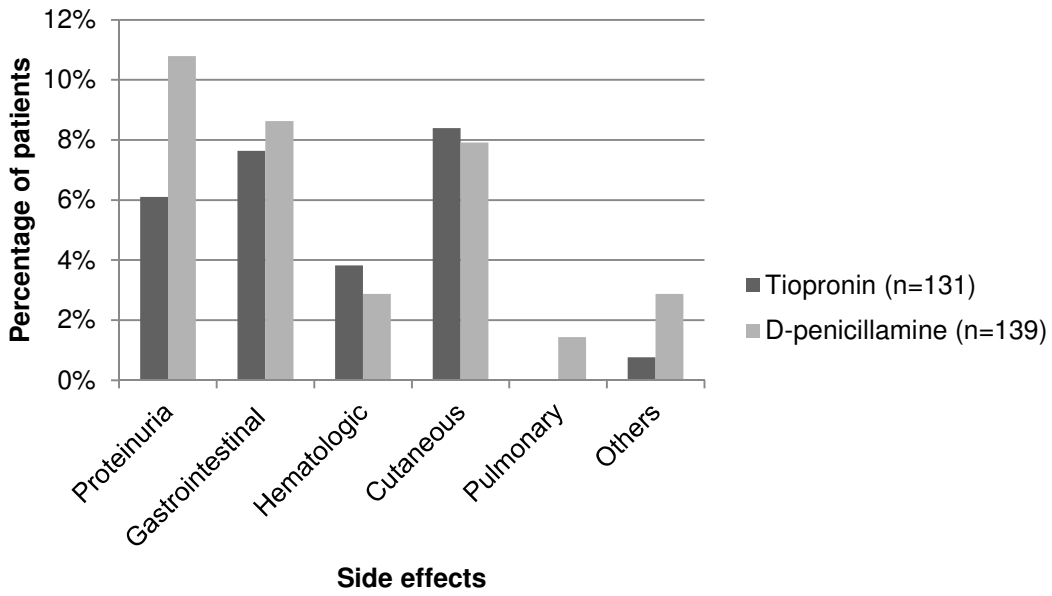
No benefit of thiols on cristalluria if U pH is high enough



Prot-Bertoye C, BJU Int, 2019

CBD side effects

- ≥ 1 side effects
  - **23.7% patients Tiopronine**
  - **30.2% patients D-penicillamine (*P*=0.23)**



Prot-Bertoye C, BJU Int, 2019

Therapeutic Strategy

Baseline Treatment
Methionin/animal protein poor diet
Diuresis > 3L/dy (2l/1.73m2 children)
NaCl <6g/dy (Na<1-1,5 mEq/Kg/d)
Alcalinization: K Citrate

↓

Stone recurrence
Cys > 1 mmol/l

↓

Reinforce baseline treatment
+ Check for compliance +++

↓

Stone recurrence
Cys > 1 mmol/l

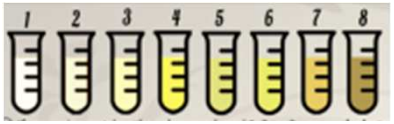
Cystine Binding Drugs

Follow up

US/low dose CT scan
24h Urines
Diuresis >3L
Na U < 100 mmol:l
Urea < 4-5 mmol/kg/dy
Cystine <1 mmol/l (250 mg/l)

Spot Urine:
Gravity ≤1.005 (or color chart)
pH U 7,5 – 8
Cristalluria negative

Patient self monitoring +++



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ERKNet working group on Cystinuria

Next Webinars

ESPN/ERKNet Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: **05 May 2020**

Speaker: **Max Liebau**

Topic: **ARPKD**

IPNA Clinical Practice Webinars

Date: **08 May 2020**

Speaker: **Katharina Hohenfellner**

Topic**: Management of Bone Disease in Cystinosis: Statement from an International Conference**

ERKNet Advanced Webinars on Rare Kidney Disorders

Date: **26 May 2020**

Speaker: **Jack Wetzels**

Topic: **Systemic Amyloidosis: A primer for the Nephrologist**

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