Welcome to

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

WEBINAR

24/01/2023

Cystinuria – adult view

Speaker: Pietro Manuel Ferraro (Rome, Italy)

Moderator: Jens König (Münster, Germany)

ERKNet
The European
Rare Kidney Disease
Reference Network

ERA
LEADING EUROPEAN NEPHROLOGY

Disclosures

- Allena Pharmaceuticals
- Alnylam
- Amgen
- AstraZeneca
- BioHealth Italia
- Gilead
- Otsuka Pharmaceuticals
- Vifor Fresenius

Layout

- Pathophysiology
- Epidemiology
- Clinical picture
- Diagnosis
- Treatment
- Follow-up

What is your main specialty?

- Pediatric nephrologist
- Adult nephrologist
- Pediatric urologist
- Adult urologist
- Other

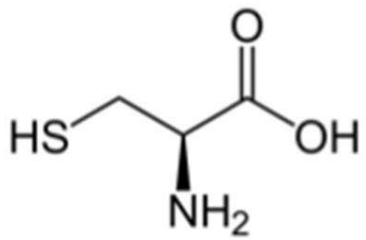
How many patients with cystinuria have you treated in the last year?

- Less than 5
- Between 5 and 10
- Between 10 and 20
- More than 20

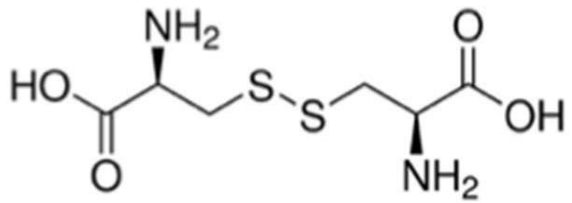
What definition best describes cystinuria?

- An X-linked condition characterized by accumulation of cystine in the cells
- An AR condition characterized by accumulation of cystine in the cells
- An AD condition characterized by abnormal urinary excretion of cystine
- An AR condition characterized by abnormal urinary excretion of cystine

Pathophysiology



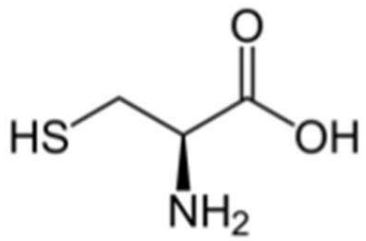
Cysteine



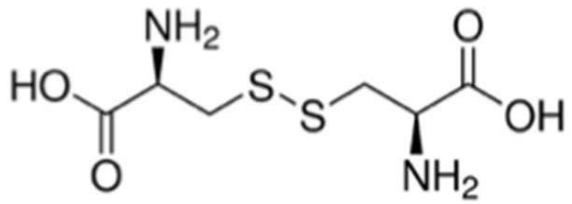
Cystine

D'Ambrosio…Ferraro, Pediatr Nephrol 2022

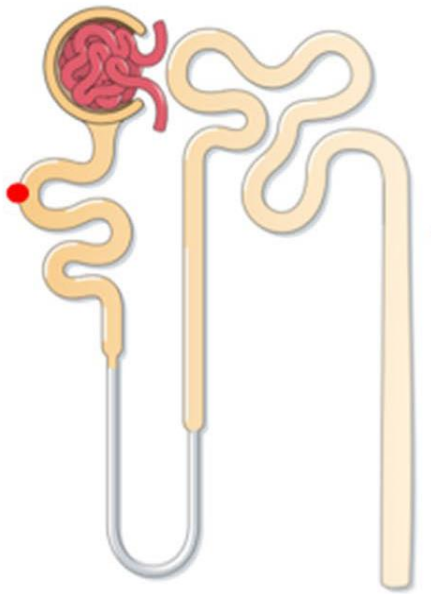
Pathophysiology



Cysteine

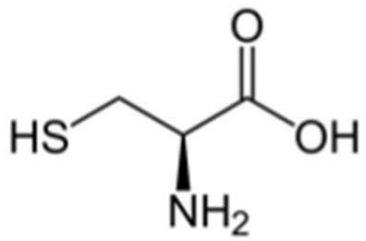


Cystine

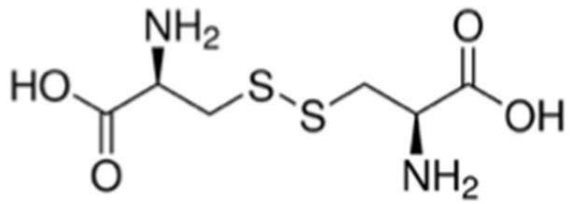


D'Ambrosio…Ferraro, Pediatr Nephrol 2022

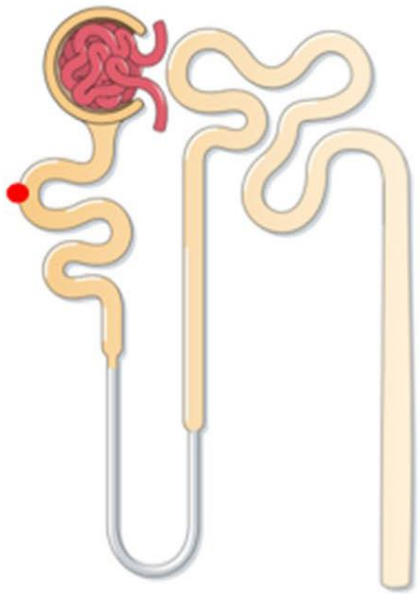
Pathophysiology

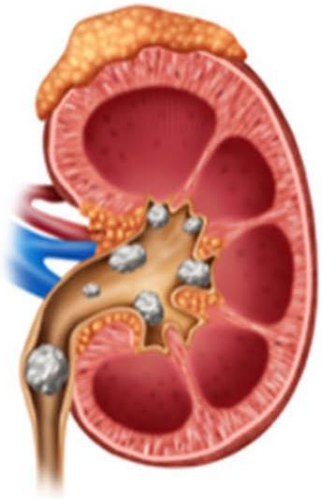


Cysteine



Cystine

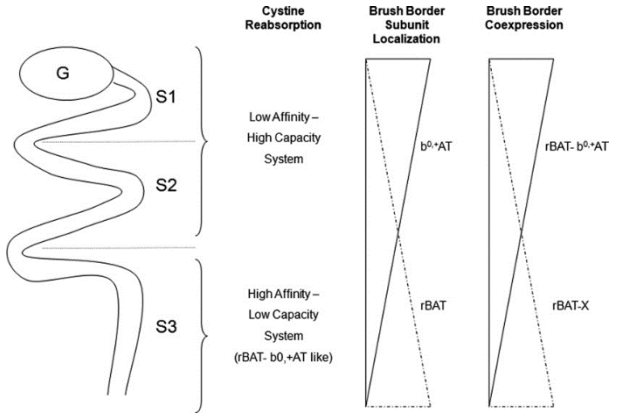




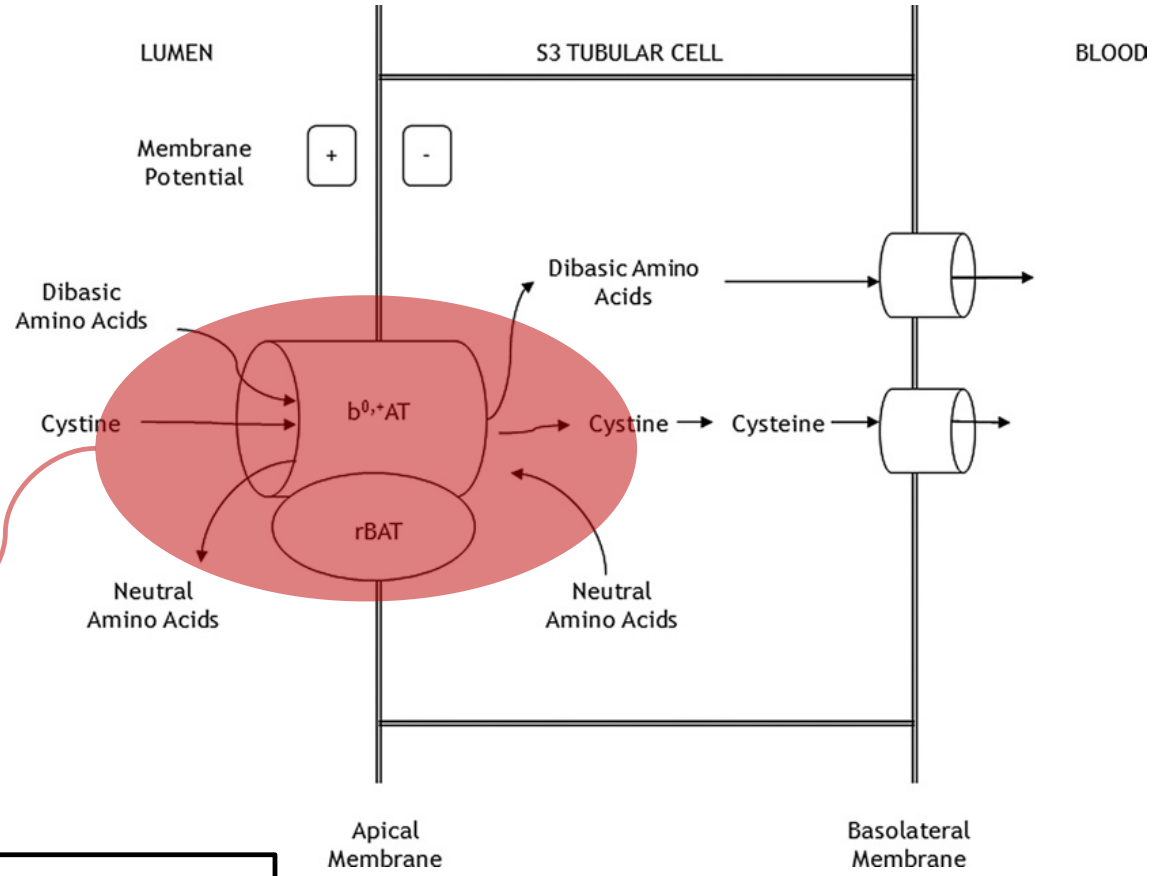
Recurrent nephrolithiasis
Renal colic
Acute kidney injury
Chronic kidney disease
Kidney failure

D'Ambrosio…Ferraro, Pediatr Nephrol 2022

Pathophysiology



- $b^{0,+}AT$ [SLC7A9] chr 9q
- rBAT [SLC3A1] chr 2p



24h uCys excretion:
0.13 mmol (30 mg) → up to 15 mmol (3,600 mg)

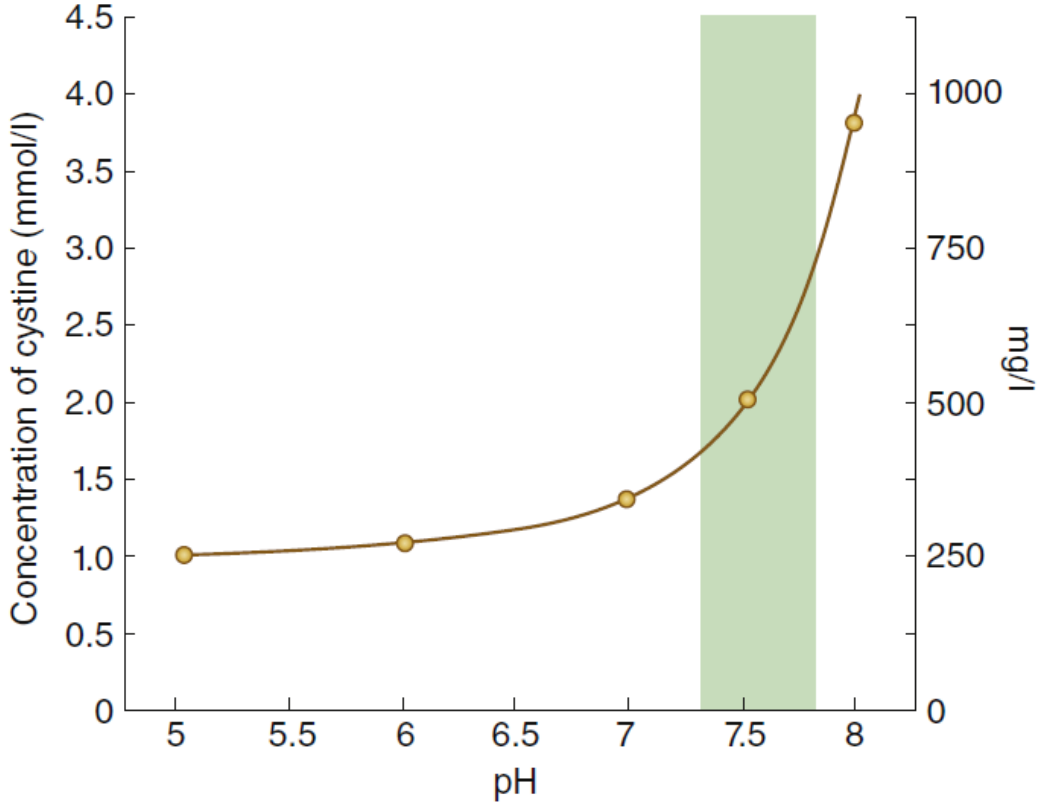
Mattoo, Semin Nephrol 2008

Pathophysiology

meeting report www.kidney-international.org

Cystinuria: clinical practice recommendation

Aude Servais[1], Kay Thomas[2], Luca Dello Strologo[3], John A. Sayer[4,5,6], Soumeya Bekri[7], Aurelia Bertholet-Thomas[8], Matthew Bultitude[2], Giovanna Capolongo[9], Rimante Cerkauskiene[10], Michel Daudon[11], Steeve Doizi[12], Valentine Gillion[13], Silvia Gràcia-Garcia[14], Jan Halbritter[15], Laurence Heidet[16], Marleen van den Heijkant[17], Sandrine Lemoine[18,19], Bertrand Knebelmann[1], Francesco Emma[20] and Elena Levtchenko[21,22]; on behalf of the Metabolic Nephropathy Workgroup of the European Reference Network for Rare Kidney Diseases (ERKNet) and eUROGEN



Servais, Kidney Int 2021

Pathophysiology

meeting report www.kidney-international.org

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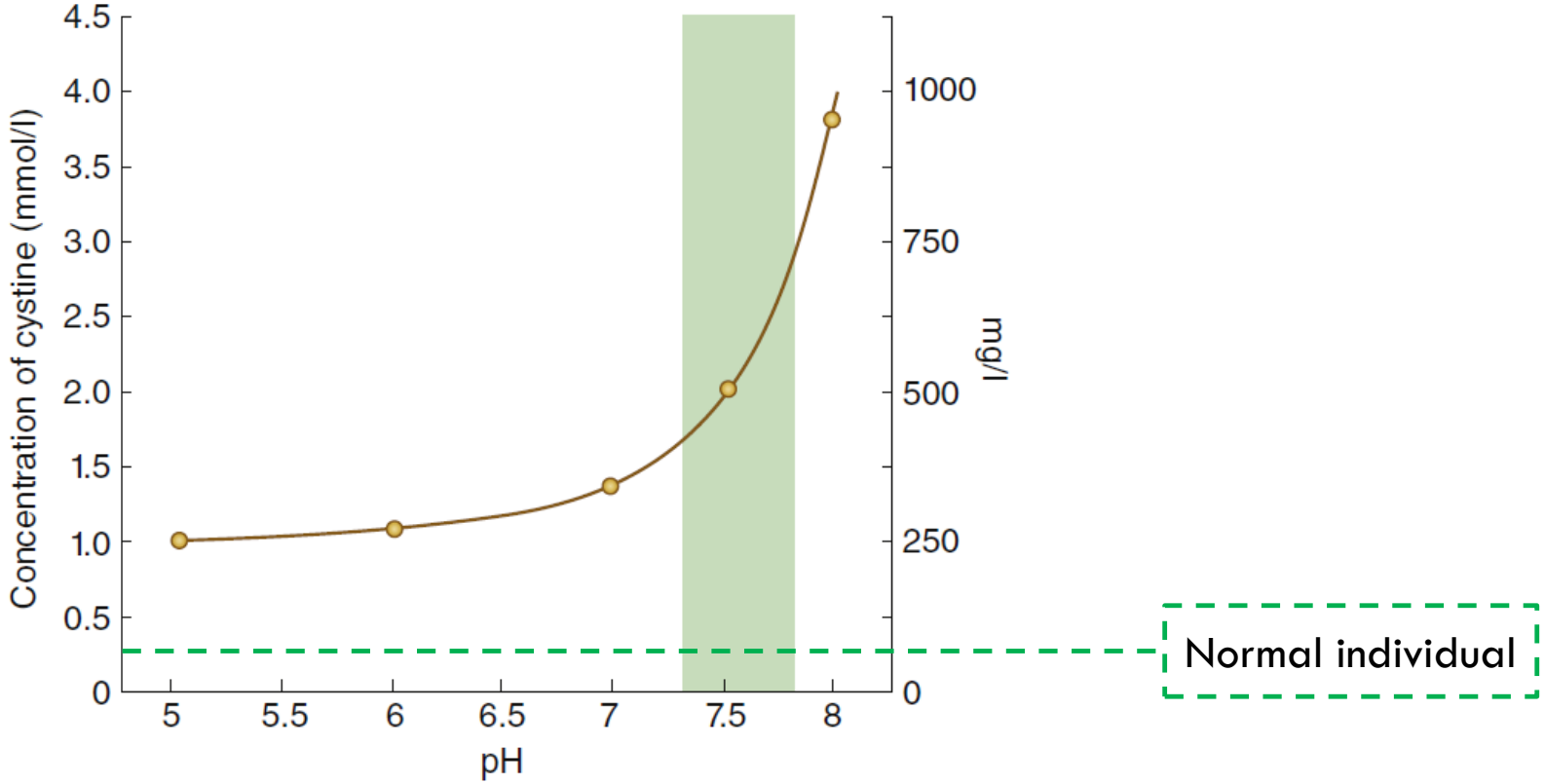

Servais, Kidney Int 2021

Pathophysiology

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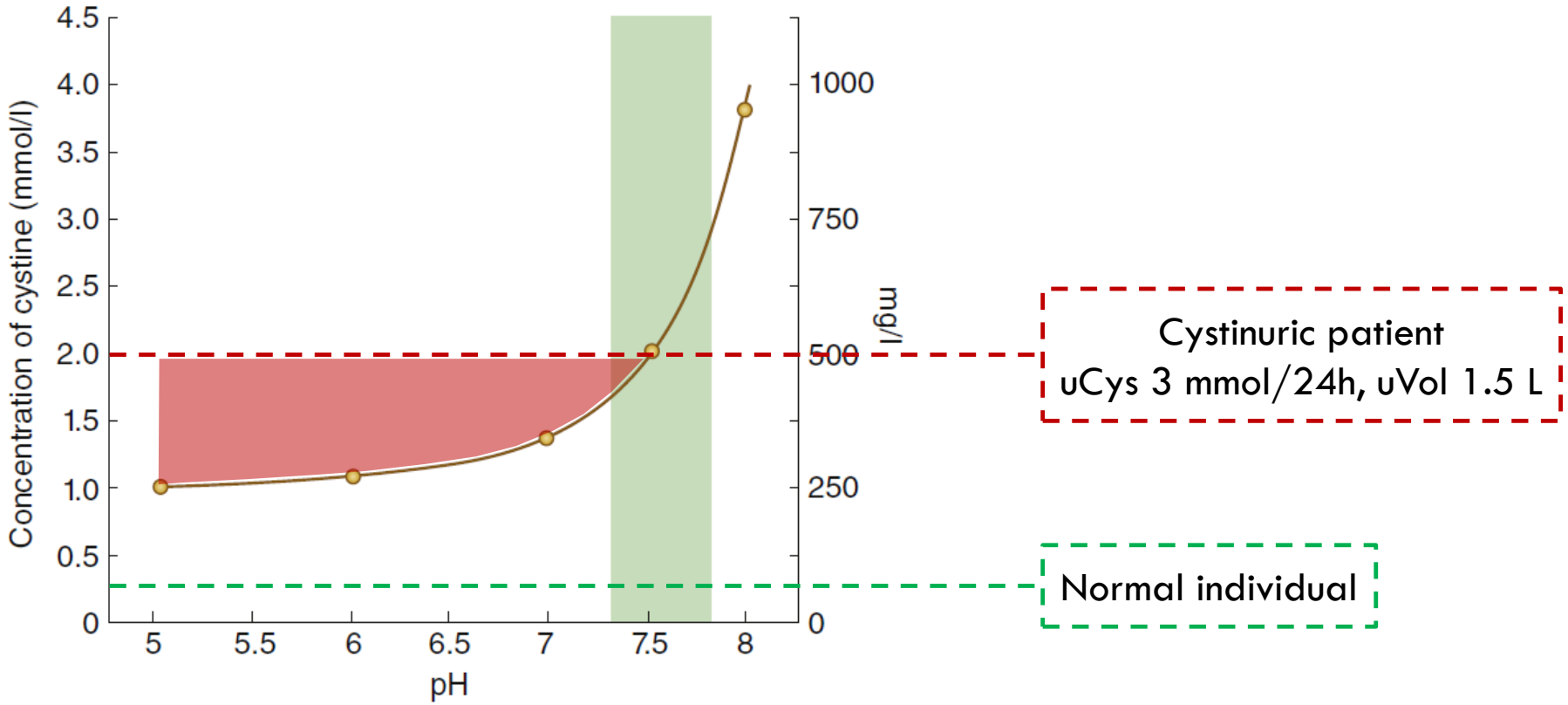

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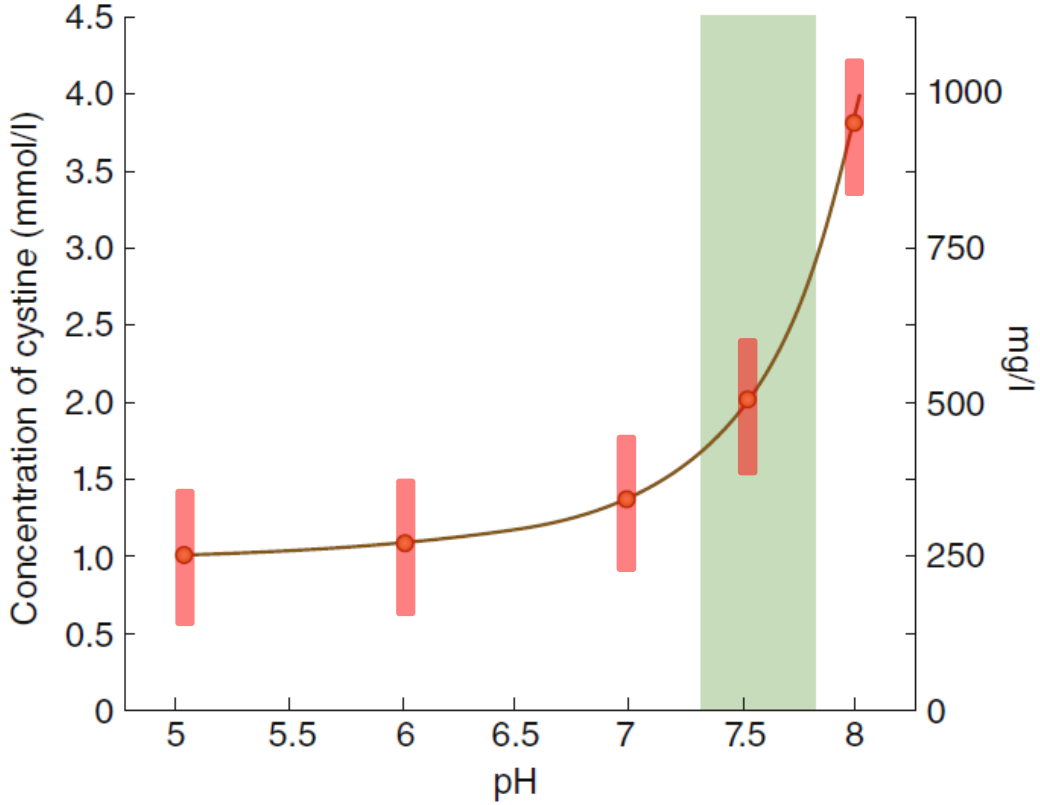
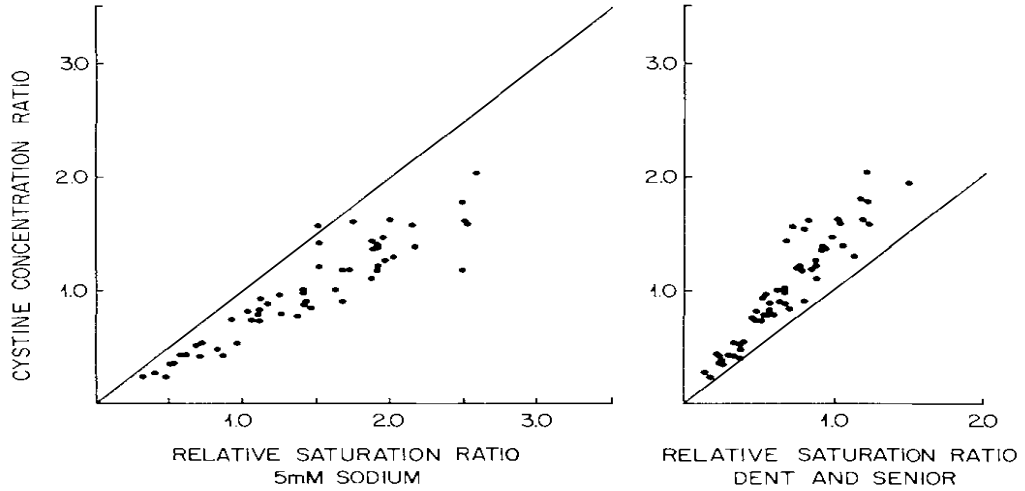


- Influence of mineral electrolytes and macromolecules
- Heterogeneous nucleation (growth of cystine crystals on crystals of a different chemical nature)



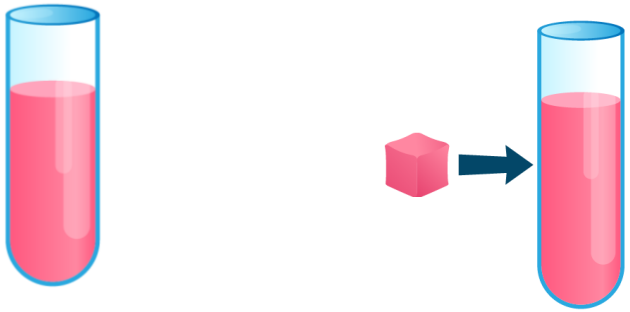
Servais, Kidney Int 2021; Pak, J Urol 1983

Pathophysiology

Cystine supersaturation ratio

Pathophysiology

Cystine supersaturation ratio



Pathophysiology

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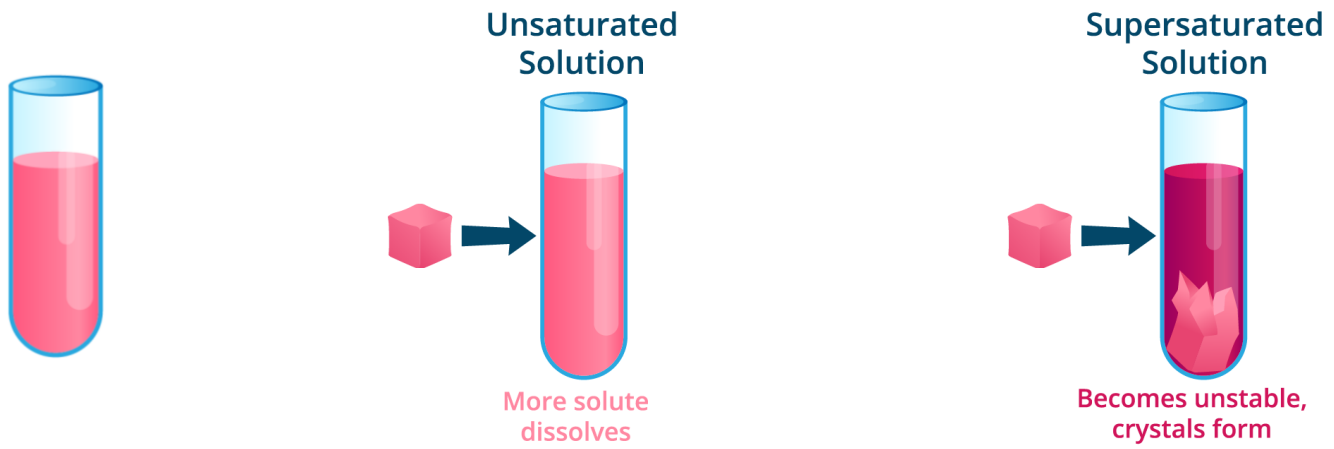

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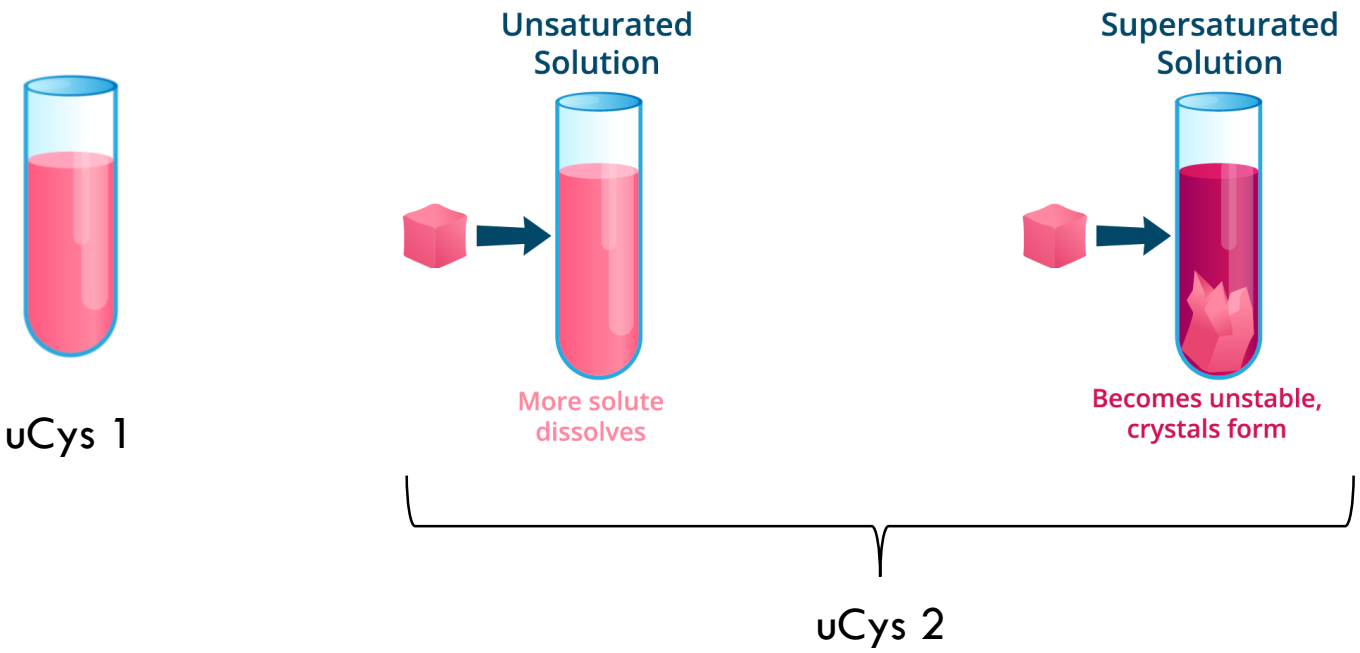

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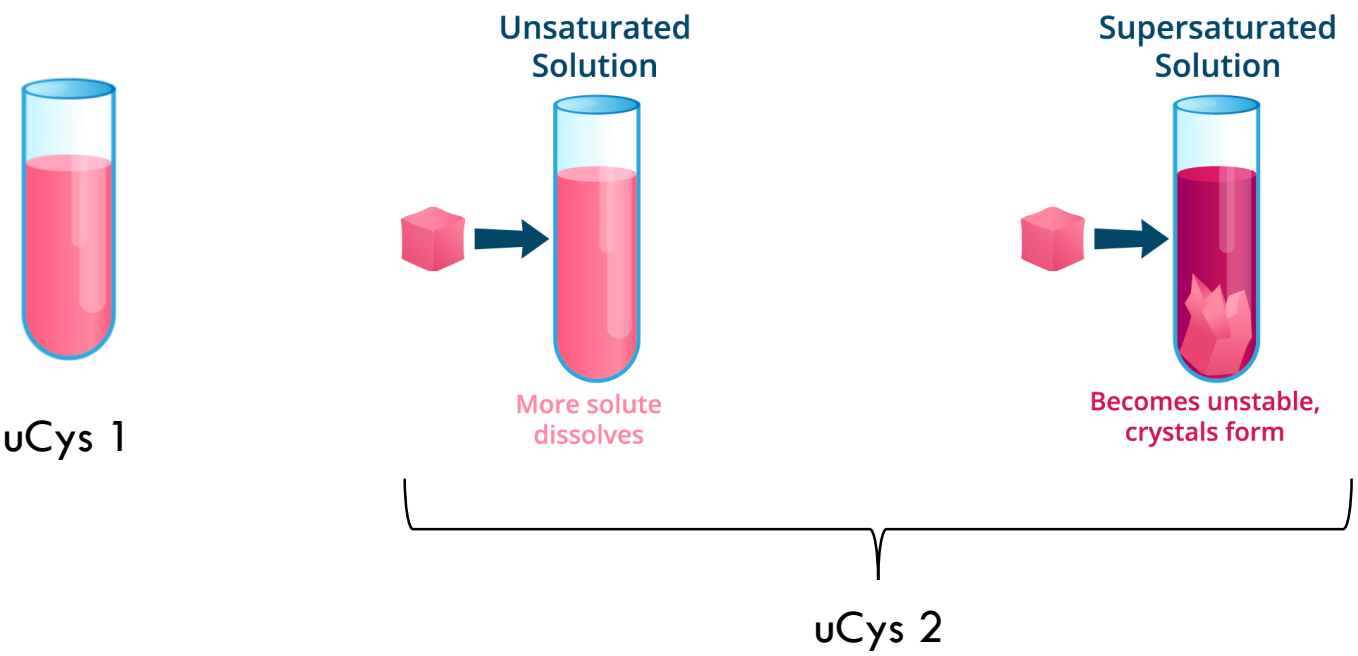


$$\frac{uCys\ 1}{uCys\ 2} < 1$$ UNSATURATED

$$\frac{uCys\ 1}{uCys\ 2} = 1$$ SATURATED

$$\frac{uCys\ 1}{uCys\ 2} > 1$$ SUPERSATURATED

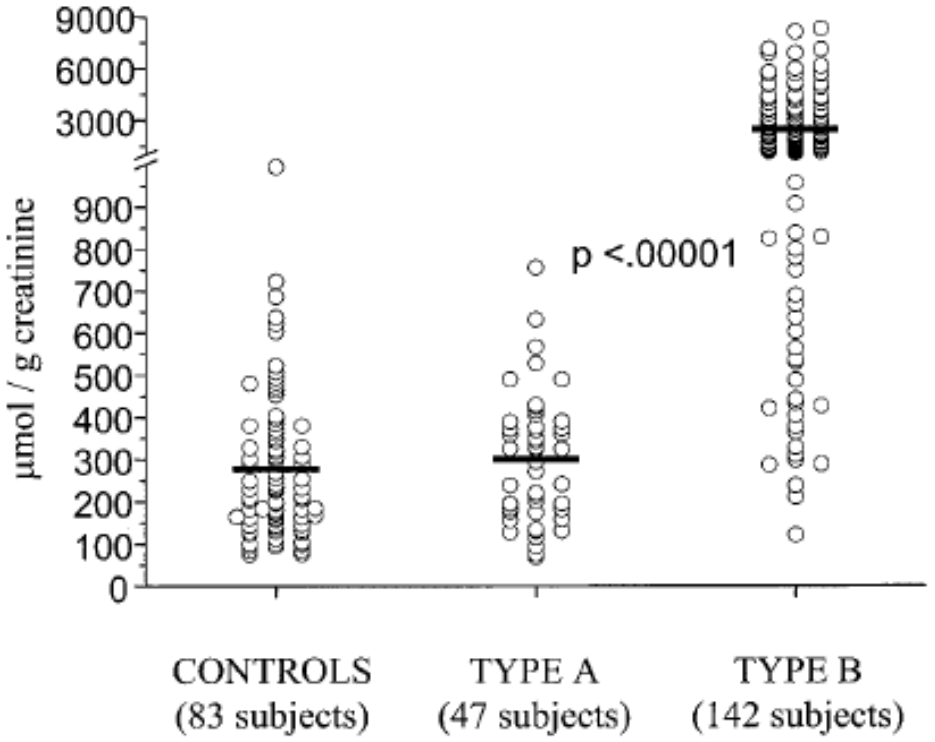
Pathophysiology

Genetics

- Autosomal recessive pattern of inheritance
- Type A (AA): biallelic mutation SLC3A1 (rBAT)
- Type B (BB): biallelic mutation SLC7A9 ($b^{0,+}AT$)
- Occasionally: co-occurrence of mutations in both genes
  - AAB, ABB associated with disease
  - AB usually not associated with disease
- Heterozigous A (A0) → normal urinary cystine excretion, but elevated for some mutations (Dup E5-E9)
- Heterozigous B (B0) → elevated urinary cystine excretion
- No clear genotype-phenotype correlation

Pathophysiology

COLA excretion in heterozygotes



Dello Strologo, J Am Soc Nephrol 2002

Epidemiology

- Worldwide prevalence ~1/7,000
- Most common cause of monogenic kidney stones
- Large ethnogeographic variation
  - 1/2,000 Eastern Mediterranean
  - 1/100,000 Sweden
- Prevalence among kidney stone formers
  - 1% adults
  - 3-10% children
- Men/Women 2:1
- Age at presentation
  - Median 22 years
  - 20-25% presentation in childhood

Chillaron, Nat Rev Nephrol 2010

Epidemiology

	Halbritter 2015	Braun 2016	Daga 2017
N (% ped)	272 (39%)	143 (100%)	65 (?)
Population	NL/NC	Age <18 y, NL/NC	Age <25 y, NL/NC*
Genetic approach	Exon sequencing (panel of 30 genes)	Exon sequencing (panel of 30 genes)	Whole-exome sequencing
Secondary causes	Excluded	Excluded	Excluded

**enrichment for recurrent disease and family history*

Halbritter, J Am Soc Nephrol 2015; Braun, Clin J Am Soc Nephrol 2016; Daga, Kidney Int 2017

Epidemiology

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**enrichment for recurrent disease and family history*

Prevalence of cystinuria	
Overall	26/480 (5.4%)
<18 yrs	12/149 (8.0%)
≥18 yrs	13/166 (7.8%)

Halbritter, J Am Soc Nephrol 2015; Braun, Clin J Am Soc Nephrol 2016; Daga, Kidney Int 2017

Clinical picture

- Kidney stones
- Chronic kidney disease

Clinical picture

Va	Cystine	Rough surface. Color: yellowish.	Section: poorly organized, sometimes a radiating organization. Color: yellowish. Concentric layers at the periphery, an unorganized core. Color: heterogeneous, cream (periphery) to yellowish (core).
Vb	Cystine	Smooth surface. Color: homogeneous, cream to yellowish.	

Kidney stones

- Composition
  - 50% pure cystine

Morphological subtype	Stone morphology		Common etiology
	Main component	**Surface**	**Section**
Cystine **Type Va**			Cystinuria
Cystine **TypeVb**			Cystinuria + inadequate diet and/or medical management, stasis

Bostrom, Acta Med Scand 1964; Daudon, Chimie 2016

Clinical picture

Kidney stones

- Composition
  - 50% pure cystine

Bostrom, Acta Med Scand 1964

Clinical picture

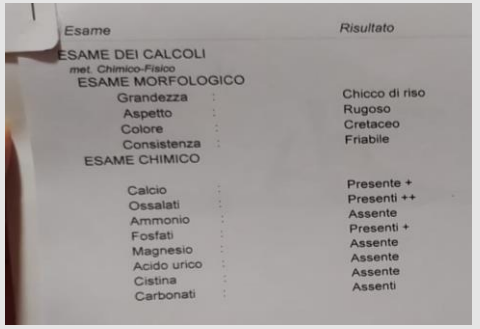
Kidney stones

- Composition
  - 50% pure cystine
  - 40% cystine + other salts
  - 10% no cystine

Bostrom, Acta Med Scand 1964

- 42 yo woman
- Recurrent kidney stones since 18 yo
- Several urological interventions
- Positive family history for stones (paternal grand-mother)

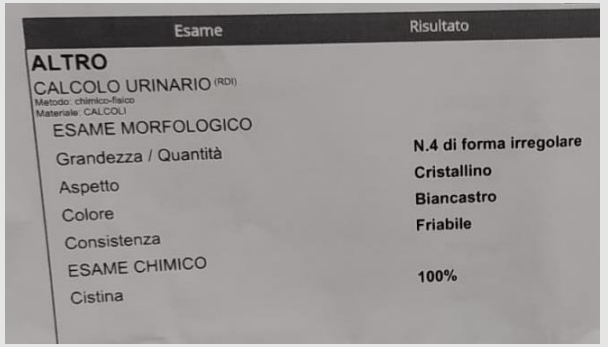
Feb 2019 (chem)



Esame	Risultato
ESAME DEI CALCOLI	
met. Chimico-Fisico	
ESAME MORFOLOGICO	
Grandezza	Chicco di riso
Aspetto	Rugoso
Colore	Cretaceo
Consistenza	Friabile
ESAME CHIMICO	
Calcio	Presente +
Ossalati	Presenti ++
Ammonio	Assente
Fosfati	Presenti +
Magnesio	Assente
Acido urico	Assente
Cistina	Assente
Carbonati	Assenti

Calcium +
Oxalate ++
Phosphate +

Sep 2022 (chem)



Esame	Risultato
ALTRO	
CALCOLO URINARIO (RDI)	
Metodo: chimico-fisico	
Materiale: CALCOLI	
ESAME MORFOLOGICO	
Grandezza / Quantità	N.4 di forma irregolare
Aspetto	Cristallino
Colore	Biancastro
Consistenza	Friabile
ESAME CHIMICO	
Cistina	100%

Cystine 100%

Dec 2022 (FT-IR)

Esame	Risultato
Calcoli	
(Metodo: spettrofotometria IR)	
Calcolo Renale	
(Metodo Spettroscopia IR)	
Lunghezza	10.0
Larghezza	5.0
Colore	Giallo
Consistenza	Friabile
Cistina	100

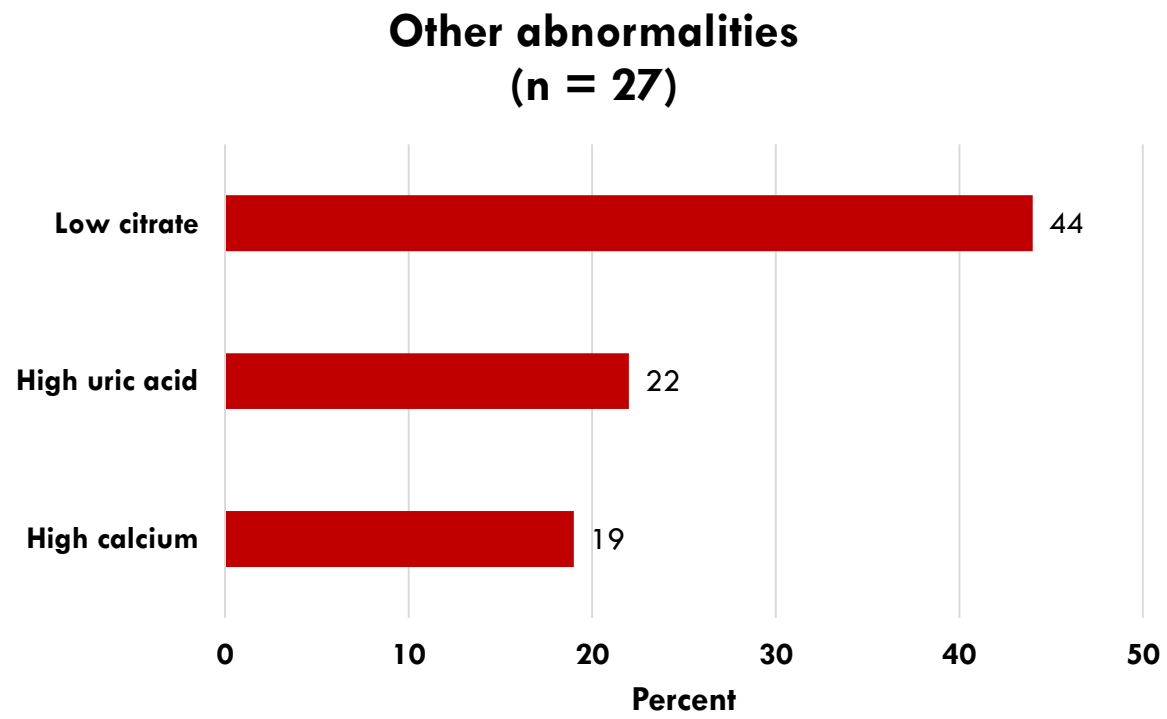
Cystine 100%
uCys: 1.6 mmol/24h

Clinical picture

THE SPECTRUM OF METABOLIC ABNORMALITIES IN PATIENTS WITH CYSTINE NEPHROLITHIASIS

KHASHAYAR SAKHAEE,* JOHN R. POINDEXTER AND CHARLES Y. C. PAK

From the Center in Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center, Dallas, Texas



Sakhaee, J Urol 1989

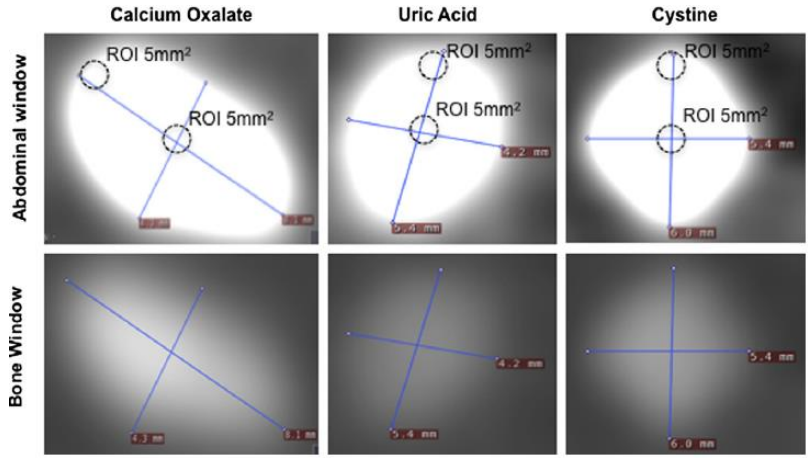
Clinical picture

Kidney stones

- Composition
  - 50% pure cystine
  - 40% cystine + other salts
  - 10% no cystine
- Recurrence rates
  - 45% at 3 months w/o treatment
  - 25% at 3 months w/ treatment
  - 83% at 5 years
- Radiographic appearance
  - Plain X-ray: not well visible (faintly radio-opaque)
  - CT scan: intermediate density (HU ~600, CaOx ~1200)

Bostrom, Acta Med Scand 1964; Leslie, StatPearls 2022

Predicting Urinary Stone Composition Based on Single-energy Noncontrast Computed Tomography: The Challenge of Cystine



Hounsfield Unit Variable	CaOx (n = 36)		UA (n = 47)		Cystine (n = 30)		CaOx vs UA	CaOx vs Cystine	UA vs Cystine
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	*P* Value		
Core HU	1099 ± 239	635 to 1522	523 ± 106	285 to 759	648 ± 122	257 to 798	<.001	<.001	<.001
Periphery HU	514 ± 116	304 to 827	382 ± 73	244 to 582	479 ± 187	204 to 776	<.001	.184	.715
Absolute HU difference	585 ± 203	227 to 945	140 ± 88	−29 to 503	169 ± 139	−82 to 400	<.001	<.001	.001
Relative HU difference (%)	52.1 ± 10.6	29.5 to 73.6	25.4 ± 13.4	−5.5 to 67	26.9 ± 21.1	−14.6 to 58.6	<.001	<.001	.002
HU density	147 ± 57	48 to 260	78 ± 45	12 to 208	51 ± 20	26.6 to 115.2	<.001	<.001	.002

CaOx, calcium oxalate; HU, Hounsfield unit; SD, standard deviation; UA, uric acid.
One-way analysis of variance—*P* <.001 for all.

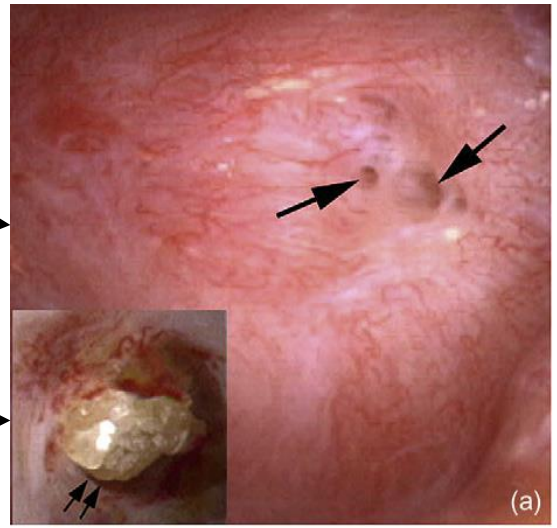
Torricelli, J Urol 2014

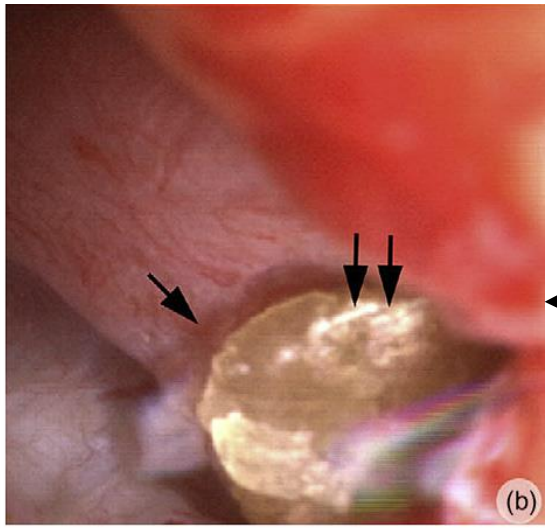
Clinical picture

Endoscopic and histologic view

enlarged openings of the ducts of Bellini

plugs of crystalline material protruding from ducts of Bellini





large masses of crystalline material lying under the urothelium

Seldin & Giebisch The Kidney 2013

Clinical picture

Endoscopic and histologic view

enlarged openings of the ducts of Bellini

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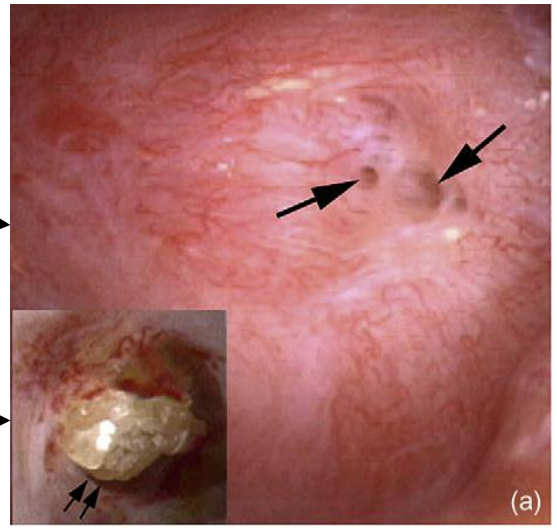
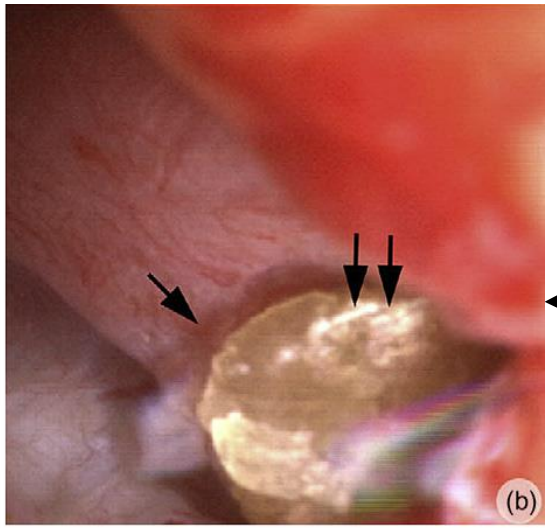




large masses of crystalline material lying under the urothelium

Intraluminal plugging in inner medullary collecting ducts (double arrow)
and thin limbs of loops of Henle (single arrow)

Seldin & Giebisch The Kidney 2013

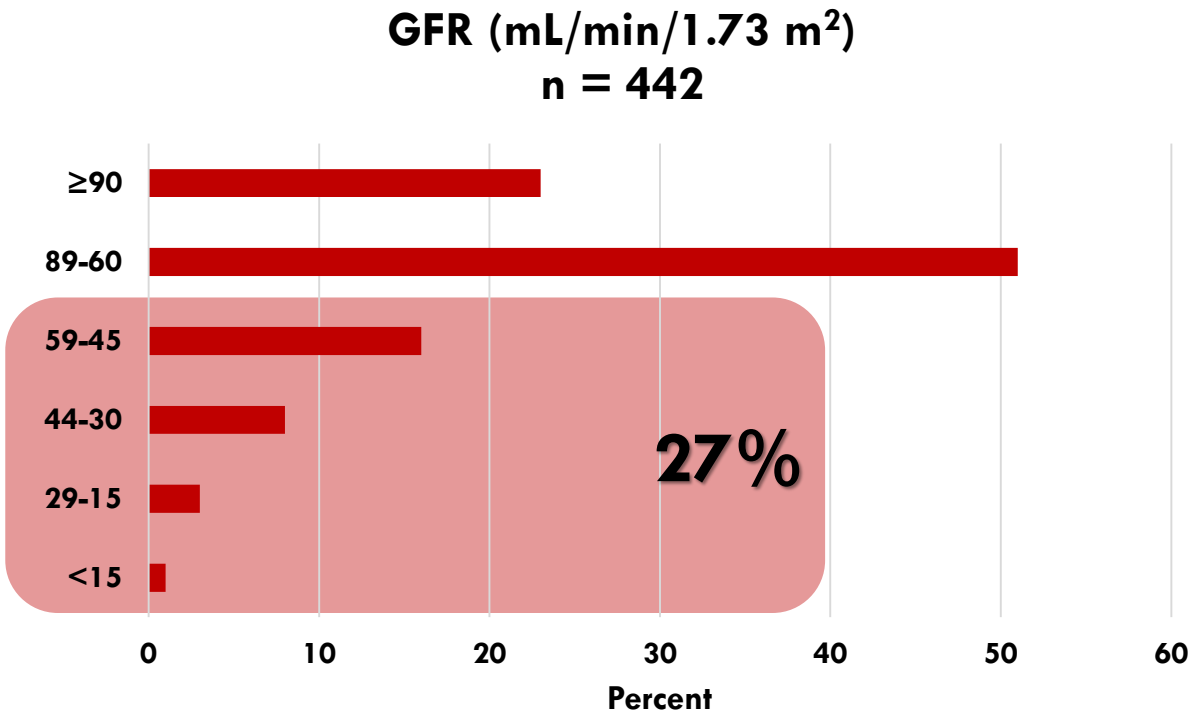
Clinical picture

- Kidney stones
- Chronic kidney disease

Clinical picture

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



Prot-Bertoye, Clin J Am Soc Nephrol 2015

Clinical picture

CKD and Its Risk Factors among Patients with Cystinuria

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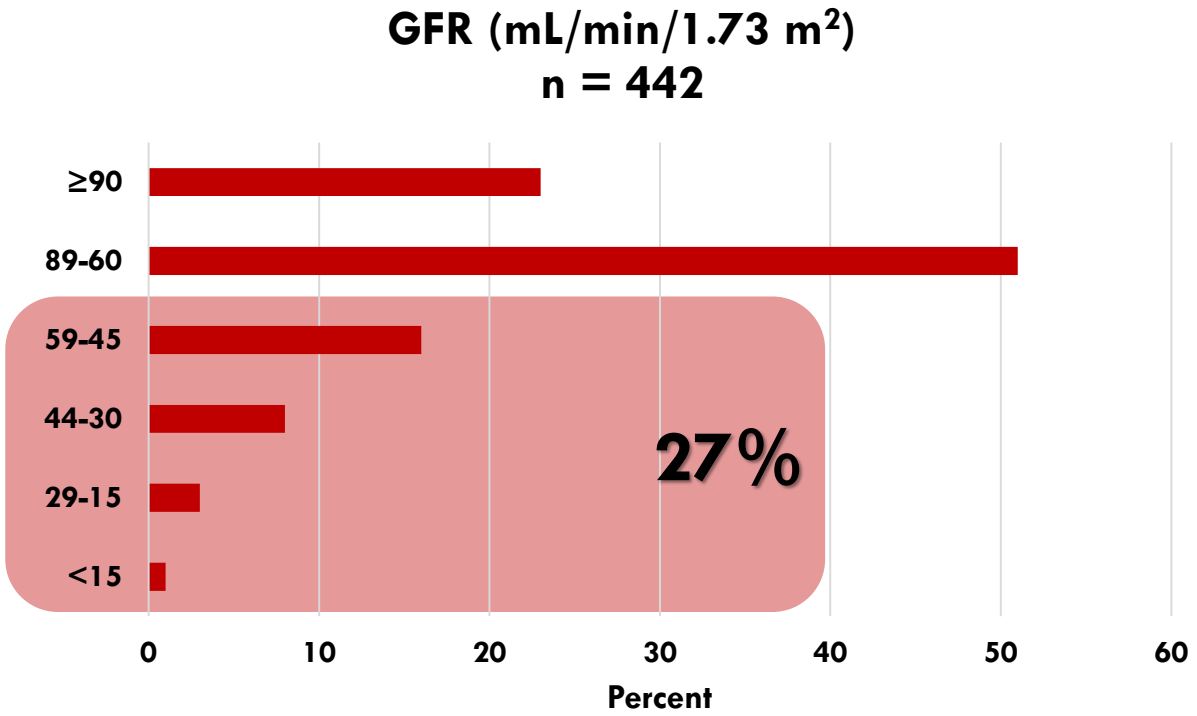


5/442 (1.1%) required RRT

OR CKD

HBP 3.3

Renal parenchyma damage 4.4

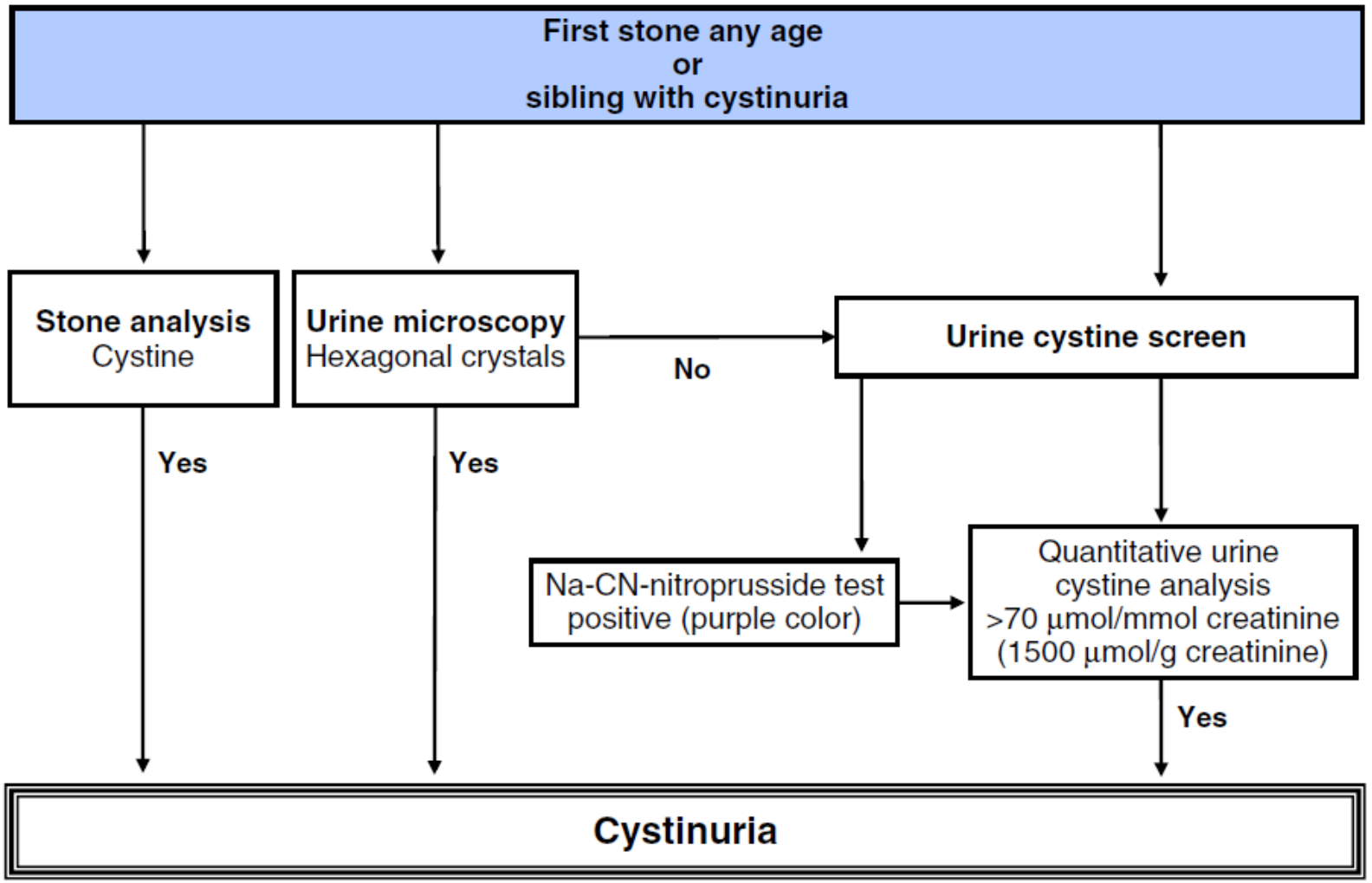
Prot-Bertoye, Clin J Am Soc Nephrol 2015

Diagnosis

- 24h urine cystine excretion (>1.6 mmol/24h)
- Stone analysis (infrared spectroscopy, X-ray diffraction)
- Cystine crystals
- Genetic analysis

in an individual with a history of kidney stones

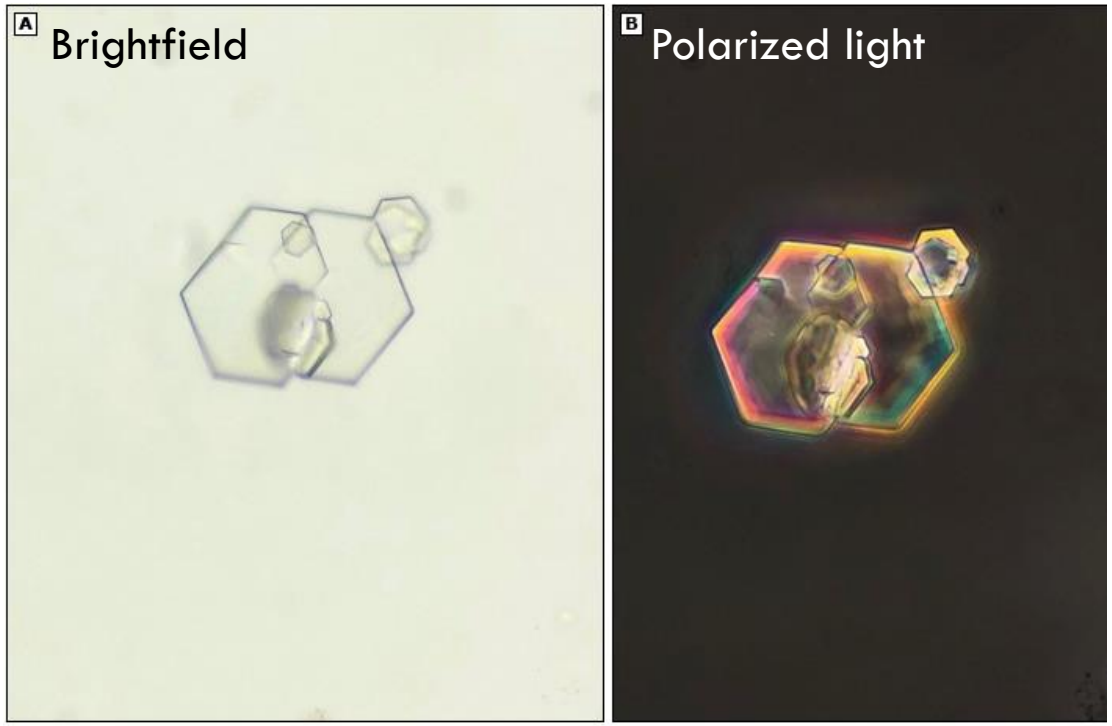
Diagnosis of Cystinuria



Edvardsson, Pediatr Nephrol 2013

Diagnosis

Cystine crystals



- On morning spot urine
- Present in 25-60% of patients
  - High specificity
  - Low sensitivity
- Crystal volume can predict stone recurrence

Daudon, Urol Res 2003

Diagnosis

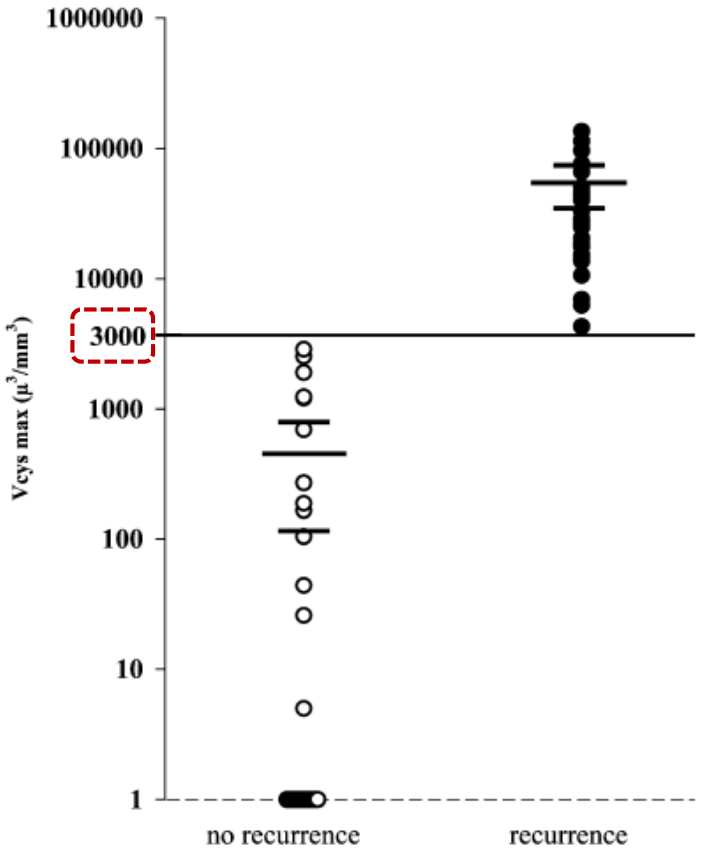
Cystine crystals

Urol Res (2003) 31: 207–211
DOI 10.1007/s00240-003-0319-0

ORIGINAL ARTICLE

Michel Daudon · Fabrice Cohen-Solal · Frédéric Barbey
Marie-France Gagnadoux · Bertrand Knebelmann
Paul Jungers

Cystine crystal volume determination: a useful tool in the management of cystinuric patients



Daudon, Urol Res 2003

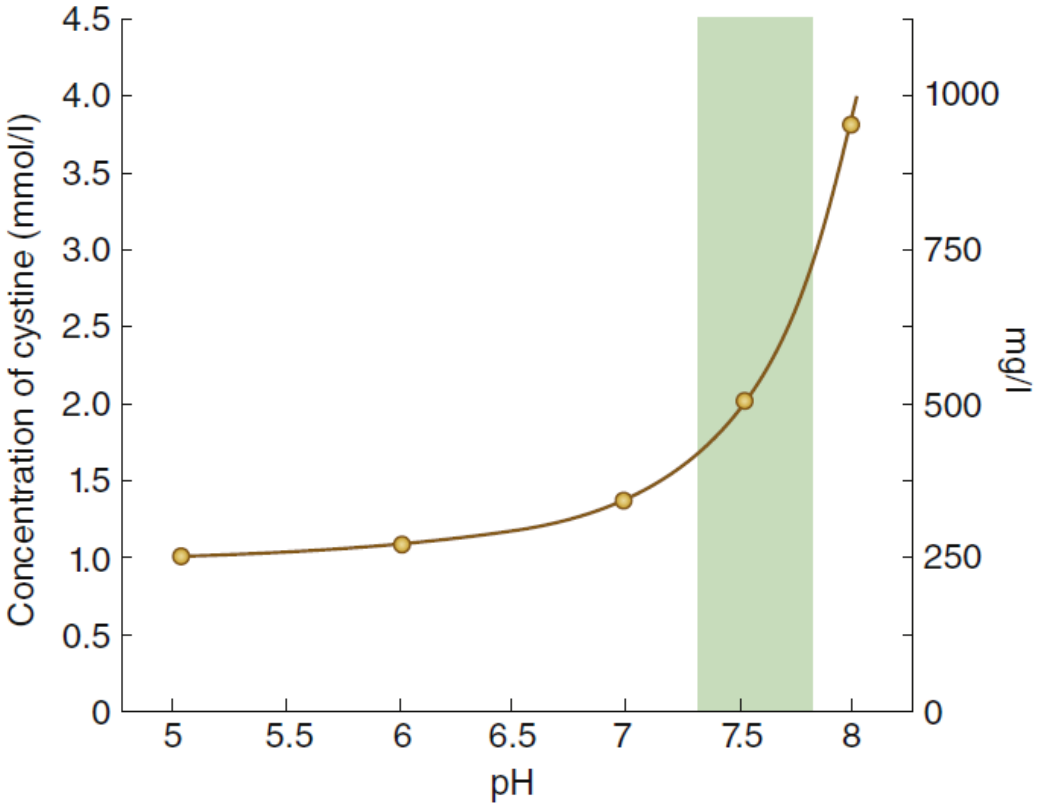
Treatment

Urological approach

- Goal: to reach the completely stone-free state
- Cystine calculi are often resistant to ESWL
- Minimally invasive procedures preferred over surgery (large or complicated stones)
- Ureteral stones and renal stones <20 mm: flexible ureteroscopy
- Renal stones >20 mm: percutaneous nephrolithotomy / ureteroscopy
- Stents: minimize dwell time due to encrustation risk (<2 weeks)

Servais, Kidney Int 2021

Treatment



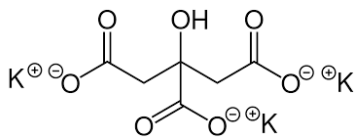
- ✓ **Reduce cystine excretion**
  - Reduce salt intake
  - Reduce animal protein intake
- ✓ **Reduce cystine concentration**
  - Increase fluid intake
- ✓ **Increase cystine solubility**
  - Increase urine pH
  - Use cystine-binding drugs

Treatment

Water intake

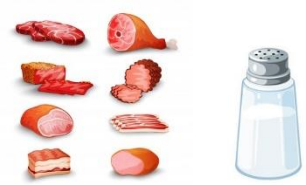
Daily water intake to obtain a urine output of at least **3 L/day**

Urinary alkalinization



60 to 80 mEq/day is recommended in three or four single doses

Diet



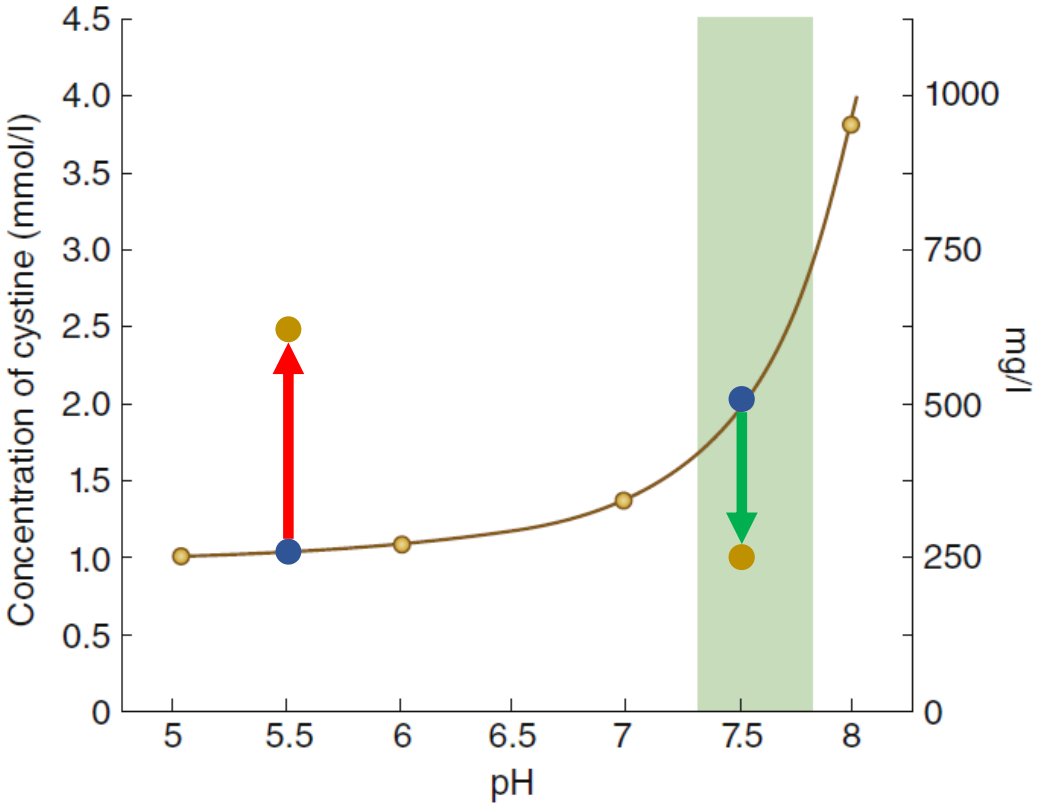
NaCl intake **<6 g/day**
It is recommended to **reduce animal protein** (or methionine-rich food)*

Food item	Content (mg/100 g)
Dried cod	2300
Horse meat	1300
Crayfish	1000
Sardines in oil	740
Tuna in oil	680
Other fish	600
Liver	600
Poultry meat	550–620
Other meat (pork, beef, mutton, and veal)	400–550
Parmesan cheese	930
Gruyère cheese	900
Emmental cheese	790
Other cheese	500–600
Eggs	390

*Avoid excessive protein restriction in children
**Risk of calcium phosphate precipitation

Servais, Kidney Int 2021

Treatment



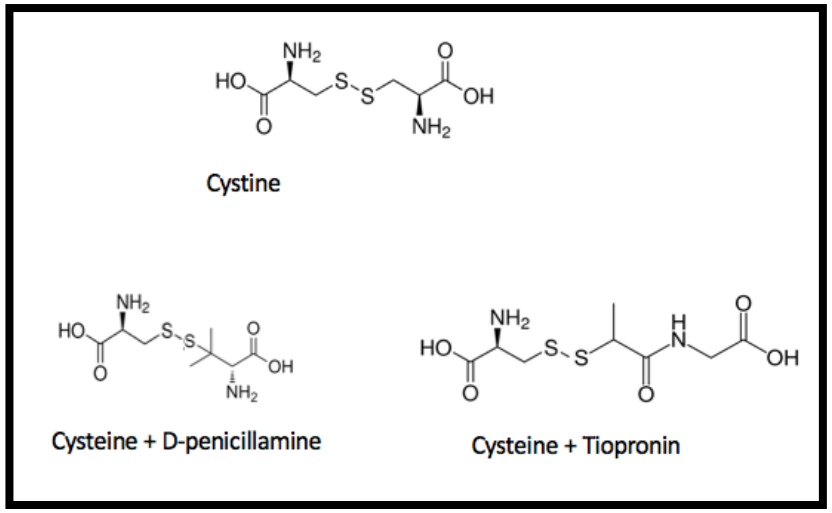
Naïve patient ➡ **Treated patient**

uCys:	3 mmol/24h	uCys:	2.7 mmol/24h
uVol:	1.2 L	uVol:	3.1 L
upH:	5.5	upH:	7.5
$[uCys]_{pt}$	= 2.5 mmol/L	$[uCys]_{pt}$	= 0.9 mmol/L
$[uCys]_{sol}$	= 1.0 mmol/L	$[uCys]_{sol}$	= 2.0 mmol/L
RSRCys	= 2.5	RSRCys	= 0.5

Hydration 3.5 L/day
Low salt / Low animal protein
Alkali

Treatment

Cystine-binding drugs



Tiopronin
800-1,500 mg/d in 3-4 doses

AEs: mucocutaneus lesions, alteration in taste, neutropenia and thrombocytopenia, gastrointestinal and liver disorders, proteinuria, described cases of MN and MCD

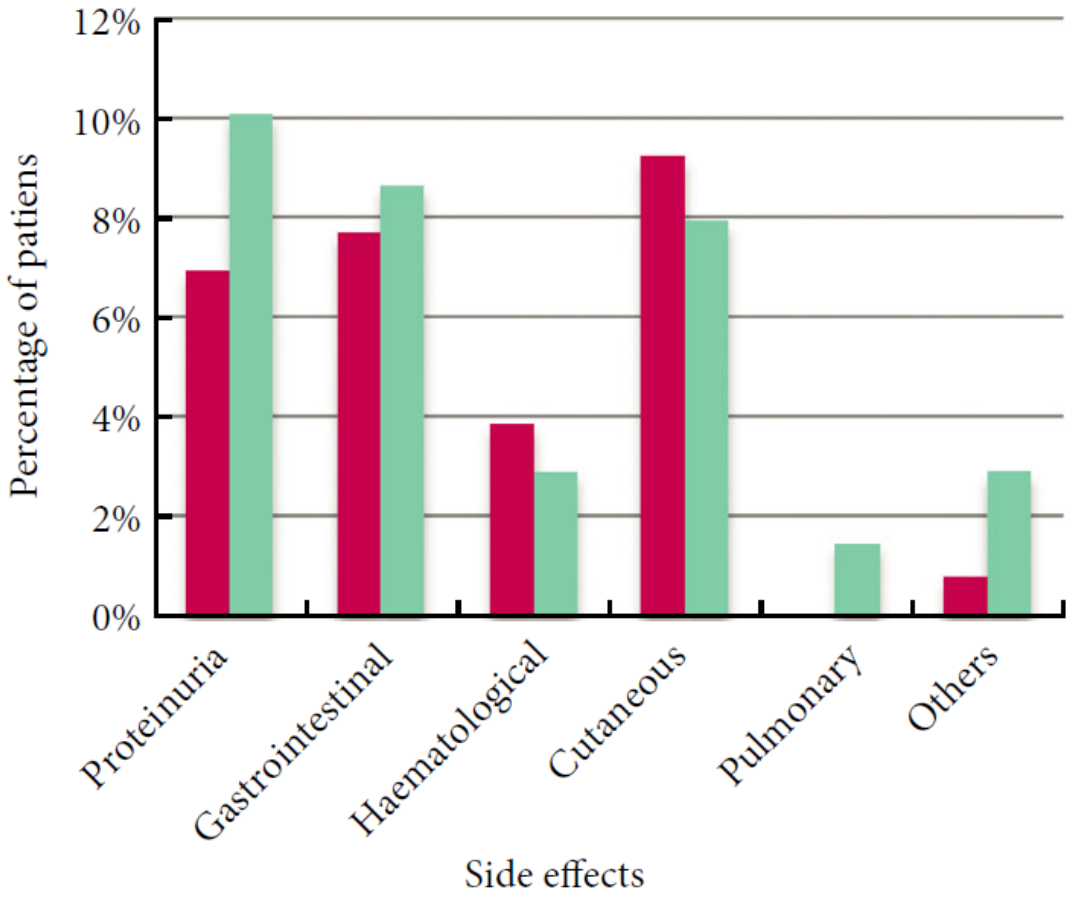
D-penicillamine
500-2,000 mg/d in 3-4 doses

AEs: fever, rash, leukopenia, aplastic anemia, hepatotoxicity, vitamin B6 deficiency, described cases of MN and RPGN

Captopril
- sulfhydryl agent of the ACEi family
- In 1987 first report of its benefits in reducing cystine excretion
- Not useful

Treatment

Cystine-binding drugs



25% adverse events
68% discontinuation

Tiopronin (n=130)

D-penicillamine (n=139)

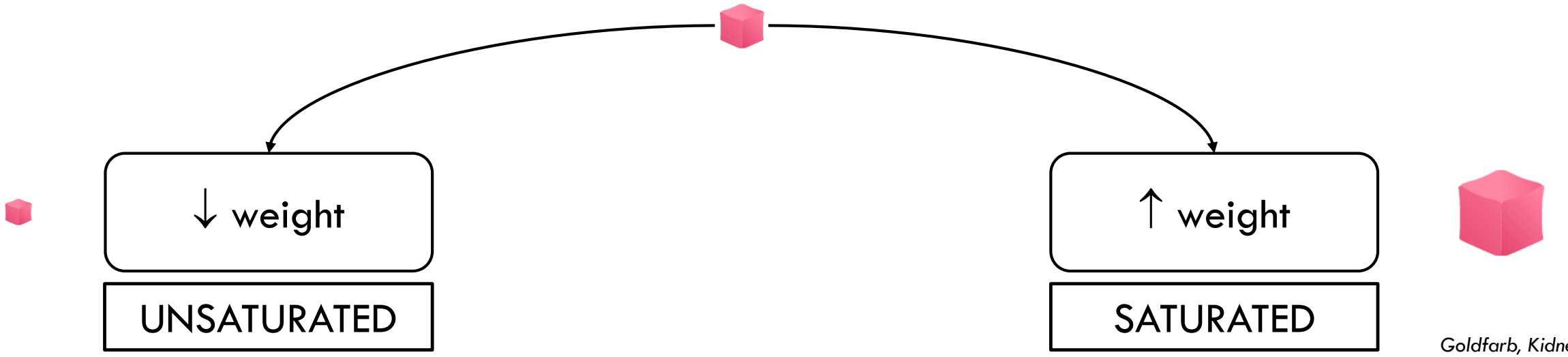
30% adverse events
85% discontinuation

Prot-Bertoye, BJU Int 2019

Treatment

Cystine capacity assessment

- Urine cystine excretion not useful to monitor disease in patients under thiol-based drugs (total cystine includes fraction bound to drug)
- A defined amount of solid cystine added to a sample of patient's urine, incubated at 37 °C for 48 hours, then solid cystine removed



Goldfarb, Kidney Int 2006

Follow-up

- Imaging
  - Protocols exist with CT, a combination of US/CT and US with CT as second-line modality
  - Frequency determined upon clinical review (every 3-12 months)
- Crystalluria
- Urinary cystine excretion and concentration
  - On 24-h urine collections (also assess sodium, sulfate and other stone-relevant parameters)
  - Daytime / nightime collections might uncover supersaturations
  - Cystine capacity assay in patients on CBD
- Complete blood cell count and urine protein excretion in patients on CBD
- Self-monitoring (urine pH and volume)

NEXT WEBINARS

21/02/23

Dysplasia and LUTO Guideline
Stefan Kohl (Cologne, Germany) and
Valentina Capone (Milano, Italy)

07/03/23

Adenine phosphoribosyltransferase deficiency: an undiagnosed cause of renal failure
Aude Servais (Paris, France)

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