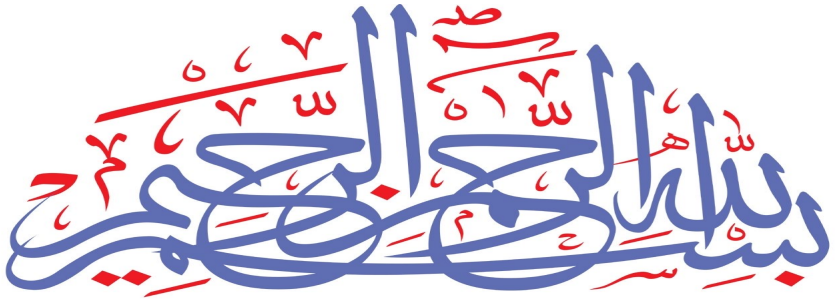


Nephrolithiasis in the hereditary and genetic disorders

Dr. Firouzeh Moeinzadeh

Associata professor of Nephrology

Isfahan University of Medical Sciences

Outlines

- **Primary hyperoxaluria**:
  - genetics, diagnosis and treatment options
- **Cystinuria**:
  - genetics, diagnosis and treatment options
- **Medullary sponge kidney**
- **Proximal tubule:**
  - Dent disease/Lowe syndrome

Introduction

- Kidney stones and many associated risk factors have strongly heritable features and tend to cluster in families
- Kidney stones develop approximately **three-fold** more frequently in individuals with a family history of kidney stones than in those without such a history
- Family history of kidney stones in **16–37%** of stone formers, yielding a **heritability of stone disease of 46–63%.**

A family-based study of metabolic phenotypes in calcium urolithiasis

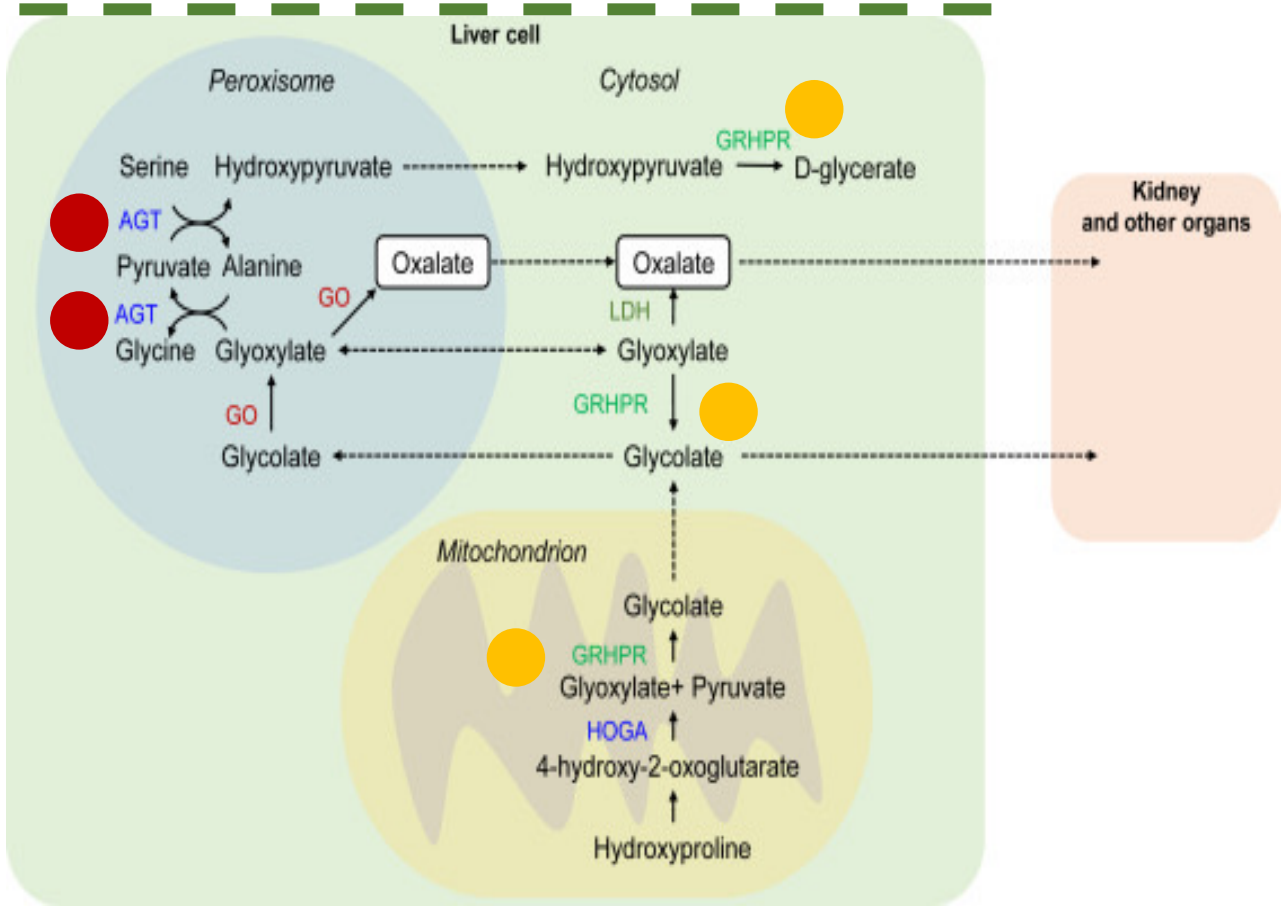
JOSÉE TESSIER, MARTIN PETRUCCI, MARIE-LUCIE TROUVÉ, LUC VALIQUETTE, GÉRALD GUAY, DENIS OUIMET, and ALAIN BONNARDEAUX

Centre de Recherche Guy Bernier, Hôpital Maisonneuve-Rosemont, Montréal, Québec, Canada

- Evaluation metabolic risk factors: **in families with at least two sibs with a history of calcium stones.**
- Increased urine calcium excretion is the only phenotype associated with a kidney stone formation.

Primary hyperoxaluria

- Primary hyperoxaluria
- **Types 1**: peroxisomal AGT deficiency
- **Types 2**: cytosolic GRHPR deficiency
- Accumulation of glyoxylate, which is converted to oxalate by LDH
- **Type 3**: defect in HOGA in mitochondria: unknown Mx



Primary Hyperoxaluria Type 1

Dawn S Milliner, MD,[1] Peter C Harris, PhD,[1] David J Sas, DO,[1] Andrea G Cogal, BS,[1] and John C Lieske, MD[1]

Created: June 19, 2002; Updated: August 15, 2024.

Natural history of primary hyperoxaluria

- Progressive decline in kidney function because of complications of nephrolithiasis (e.g., urinary obstruction, infection), nephrocalcinosis
- Other organ and tissue damage from calcium oxalate deposition (i.e., "oxalosis")

Clinical Presentations

Age at Presentation	% of All PH1	Initial Manifestations			
		Nephrolithiasis	Nephrocalcinosis	Kidney function	Oxalosis
Infantile onset (age <12 mos)	10% [1]	±	+++	Advanced CKD or ESKD	+++
Childhood/adolescence (ages 1-17 yrs)	70%	+++	+	Normal-to-moderate reduction	Only occurs w/ESKD
Adulthood (age ≥18 yrs)	20%	+++	++ w/advanced CKD or ESKD	Mild-to-moderate reduction; some w/ ESKD	Only occurs w/ESKD

Adult Onset (age ≥18 years)

- PH1 is not correctly diagnosed in 20%-50% of individuals with adult-onset disease until later stages of CKD or after kidney failure
- In ~ 10% of these adults the diagnosis of PH1 is only first considered following recurrent disease in a transplanted kidney when an allograft biopsy reveals calcium oxalate crystals by graft loss
- Most manifestations of oxalosis are **slowly reversible** following successful liver and kidney transplantation, mobilization of oxalate tissue deposits poses risk of oxalate injury to the transplanted kidney.

Oxalosis in PH1

- **Oxalosis:** complication of PH1 at any age **when eGFR <30 mL/min/1.73 m²**
- Progressive oxalosis, observed over time in most individuals with PH1 who are on dialysis, eventually leads to death.
  - **Bone.** oxalate osteodystrophy characterized by bone pain, pathologic fractures, growth delay.
  - **Retina.** frequent in **infants** with PH1 in kidney failure. less common in **adults**, typically do not cause visual impairment.
  - **Heart.** Cardiomyopathy resulting in heart failure; arrythmias and heart block

less common clinical manifestations of oxalate deposition

- Bone marrow
- Refractory hypotension
- Vascular involvement
- Peripheral neuropathy
- Cerebral infarcts
- Dental pain and root resorption
- Hypothyroidism

PH diagnosis

KIDNEY STONE + NORMAL KIDNEY FUNCTION

- Calcium oxalate stones in children, recurrent calcium oxalate stones or history of stones prior to age 21 yrs in adults, or nephrocalcinosis
- Predominantly calcium oxalate stones
- Family member with childhood stones, recurrent calculi, or unexplained CKD/kidney failure
- Family member with PH

Urine oxalate >0.5 mmol (45 mg)/1.73 m^2/24 Hours* OR random urine oxalate/urine creatinine > normal**

Confirm high urine oxalate with repeat testing and measure urine metabolites if available (glycolate, L-glycerate, 4-hydroxy-2 oxoglutarate)***

Secondary causes present?

- Malabsorption
- Gastrointestinal Disease
- Very high oxalate and low calcium diet
- Premature infant

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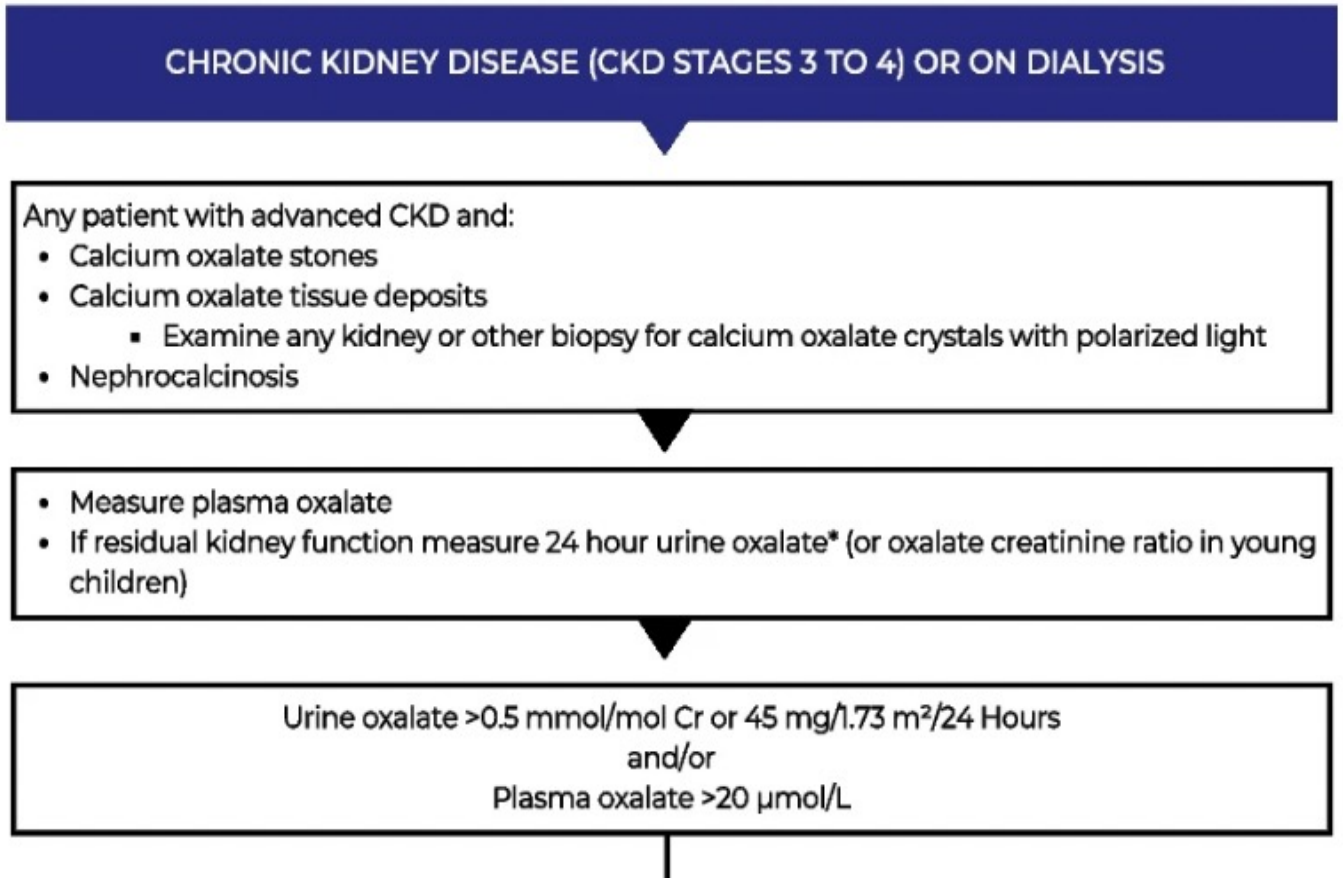
Primary Hyperoxaluria Type 1: Supportive Laboratory Findings

Laboratory Test	Constraints	Findings in PH1	Comments
Urine oxalate, 24-hr collection [1]	All individuals where possible	UOx >0.5 mmol/24 hours Uox>50mg/1.73m^2	• Must be corrected to BSA 1.73 m^2 in children • At least 2 collections required to confirm abnormality • Less reliable when eGFR <30 mL/min/BSA • Data for normal values for children age <2 yrs are limited.
Urine oxalate:creatinine, spot urine specimen [1]	Young children or others in whom 24-hr collection is difficult	UOx > normal range for age [2]	At least 2 collections to confirm abnormality
Plasma oxalate concentration	When eGFR <30 mL/min/1.73 m^2	• POx >20 is consistent w/ PH1. • POx >50 µmol/L is strongly suggestive of PH1 [Perinpam et al 2017] [3, 4]	• Plasma samples require special handling. • Results vary by method. • Available only in specialty labs
Kidney stone analysis	When stone is available	100% calcium oxalate monohydrate	Suggestive of but not specific for PH1

Normal Spot Urine Oxalate : Creatinine Ratio by Age

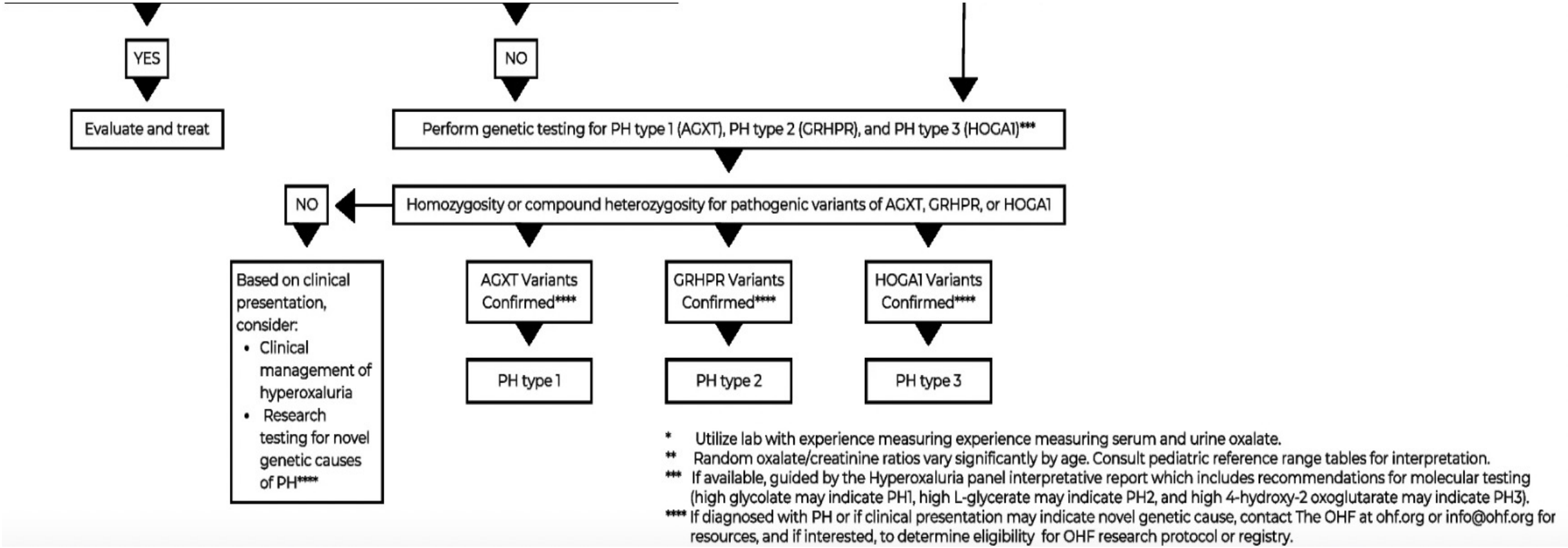
Age	mmol/mmol	mg/mg
<6 months	<0.37	<0.29
6-23 months	<0.26	<0.20
2-5 years	<0.14	<0.22
6-12 years	<0.08	<0.06
>13 years	<0.04	<0.03

PH diagnosis



Evaluations Following Initial Diagnosis

- When CKD is stage> 3b, evaluate for systemic oxalate deposits:
  - **Bone imaging**: sclerosis and/or pathologic fractures
  - **Ophthalmologic** examination: visual acuity & retinal examination
  - **Echocardiography** for evidence of cardiomyopathy
  - **Electrocardiogram** for conduction disturbances
  - **CBC** for evidence of anemia


YES
NO
Evaluate and treat
Perform genetic testing for PH type 1 (AGXT), PH type 2 (GRHPR), and PH type 3 (HOGA1)***
NO
Homozygosity or compound heterozygosity for pathogenic variants of AGXT, GRHPR, or HOGA1
Based on clinical presentation, consider:
• Clinical management of hyperoxaluria
• Research testing for novel genetic causes of PH****
AGXT Variants Confirmed****
GRHPR Variants Confirmed****
HOGA1 Variants Confirmed****
PH type 1
PH type 2
PH type 3
* Utilize lab with experience measuring experience measuring serum and urine oxalate.
** Random oxalate/creatinine ratios vary significantly by age. Consult pediatric reference range tables for interpretation.
*** If available, guided by the Hyperoxaluria panel interpretative report which includes recommendations for molecular testing (high glycolate may indicate PH1, high L-glycerate may indicate PH2, and high 4-hydroxy-2 oxoglutarate may indicate PH3).
**** If diagnosed with PH or if clinical presentation may indicate novel genetic cause, contact The OHF at ohf.org or info@ohf.org for resources, and if interested, to determine eligibility for OHF research protocol or registry.

Genetic Testing

- The diagnosis of PH1 is **established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in AGXT identified by molecular genetic testing.
- Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing).

The genetics of kidney stone disease and nephrocalcinosis

Article *in* Nature Reviews Nephrology · December 2021

DOI: 10.1038/s41581-021-00513-4

Molecular Genetic Testing Used in Primary Hyperoxaluria Type 1

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
AGXT	Sequence analysis [3]	>97% [4]
	Gene-targeted deletion/duplication analysis [5]	<3% [6]

Genotype-Phenotype Correlations

- **Pyridoxine-responsive variants.**
- Pyridoxine (vitamin B_6), a cofactor for AGT.
- Individuals **homozygous** for **3** pathogenic variants (p.Phe152Ile, p.Gly170Arg, or p.Ile244Thr) : treated with pharmacologic doses of pyridoxine
- **Heterozygotes** for p.Phe152Ile, p.Gly170Arg, or p.Ile244Thr and a non-pyridoxine-sensitive pathogenic variant developed kidney failure at a **slightly younger age**

Treatment: Pyridoxine (vitamin B_6)

- A starting pyridoxine dose of 5 mg/kg/day is recommended.
- Stepwise increases in pyridoxine dose to a maximum of 10-20 mg/kg/day with assessments of response by measurement of urine oxalate excretion at each step determines the minimum effective dose.
- Continuation of Tx:
  - Indefinitely
  - Until successful orthotopic liver transplantation

Pyridoxine (vitamin B_6) response

- Pyridoxine response: comparing the 24-hour urine oxalate excretion rate before treatment and **after at least 3 months** of pyridoxine treatment at a **minimum dose of 5 mg/kg/day**.
- **Reduction of ≥30%** or **normalization** of urinary oxalate excretion while receiving pyridoxine indicates responsiveness.
- Most individuals who are pyridoxine responsive show maximum benefit at a dose of 5-8 mg/kg/day.

Primary Hyperoxaluria Type 1

Dawn S Milliner, MD,[1] Peter C Harris, PhD,[1] David J Sas, DO,[1] Andrea G Cogal, BS,[1] and John C Lieske, MD[1]

Created: June 19, 2002; Updated: August 15, 2024.

Primary Hyperoxaluria: Supportive Care

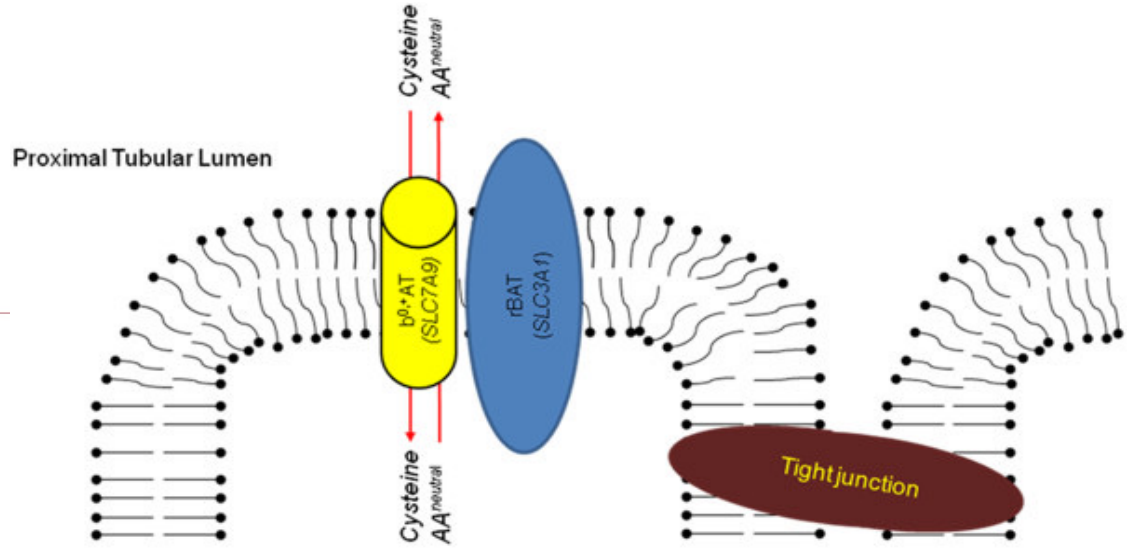
Objective	Treatment	Consideration/Other
Prevent crystal injury to kidneys by ↓ crystal formation	• Maintain high oral fluid intake to assure good urine volume. • Use oral citrate or pyrophosphate to inhibit calcium oxalate crystal formation.	Infants or small children may need gastrostomy tube placement.
Reduce stone formation	• Maintain high urine volume. • Minimize urine oxalate concentration. • Optimize urine citrate.	Use imaging studies at regular intervals to guide mgmt.
Reduce stone-related kidney damage	• Consult w/urologist experienced in mgmt of PH. • Ureteroscopic mgmt of symptomatic stones preferred when appropriate.	• Prompt attention to pain or other symptoms suggesting infection or possible urinary obstruction. • Use imaging studies at regular intervals to guide mgmt.
Preserve kidney function	• Avoid dehydration. • Avoid nephrotoxins that can cause kidney injury (e.g., NSAIDs).	Use IV fluid if needed to assure high urine volume (e.g., during vomiting or diarrhea).
Prevent systemic oxalosis	• Monitor plasma oxalate concentration during transient or permanent periods of low GFR. • Initiate dialysis promptly to ↓ oxalate concentration. [1, 2]	Dialysis, most often used as a bridge to kidney recovery or transplantation, often requires ≥4 dialysis sessions per week to maintain plasma oxalate concentrations that minimize risk of oxalosis. [2, 3]

Primary Hyperoxaluria: Targeted Therapies

Treatment Class	Treatment	Therapy Candidates	Mechanism	Comment
Small molecule therapy	Pyridoxine (vitamin B_6 analog)	Persons w/missense *AGXT* variants, esp homozygotes for p.Phe152Ile, p.Gly170Arg, & p.Ile244Thr (See Genotype-Phenotype Correlations & Table 10.)	Enhances residual activity of AGT (a pyridoxal 5'-phosphate-dependent enzyme) [1]	• ~30%-50% of individuals w/PH1 are pyridoxine responsive. • Since there are multiple mechanisms of pyridoxine response & only a few pathogenic variants have been tested, a trial of pyridoxine should be considered in all persons w/1 or 2 missense *AGXT* pathogenic variants, incl those w/advanced CKD or kidney failure. [2]
Gene therapy (RNAi)	Lumasiran (Oxlumo®)	Effective in all persons w/PH1, independent of specific *AGXT* pathogenic variants	siRNA therapeutic agent that ↓s glyoxylate substrate available for metabolic conversion to oxalate by targeted reduction of hepatic glycolate oxidase	• FDA & EMA approved for persons of all ages • Experience using lumasiran in persons w/advanced CKD, on dialysis, or following kidney transplantation alone is limited.
	Nedosiran (Rivfloza®)	Effectiveness demonstrated in PH1 independent of specific *AGXT* pathogenic variants	siRNA therapeutic agent that ↓s conversion of glyoxylate to oxalate by targeted reduction of hepatic LDHA	FDA approved in persons w/PH1 age >9 yrs w/eGFR >30 mL/min/1.73 m^2
Organ transplantation	Liver transplant	Persons w/GFR <25-30 mL/min/1.73 m^2	Liver transplantation restores normal AGT activity.	When kidney replacement therapy is needed, the decision needs to be made between kidney transplant alone or liver & kidney transplant simultaneously. [3]

Cystinuria

- A monogenic disease characterized by recurrent nephrolithiasis often starting in childhood.
- An autosomal recessive inheritance
- Autosomal dominant inheritance with incomplete penetrance has also been reported
- Gene Defects: SLC3A1 or SLC7A9



Turkish Archives of Pediatrics

REVIEW
DOI: 10.5152/TurkArchPediatr.2022.22105

Cystinuria: An Overview of Diagnosis and Medical Management

REVIEW: GENETICS OF UROLITHIASIS

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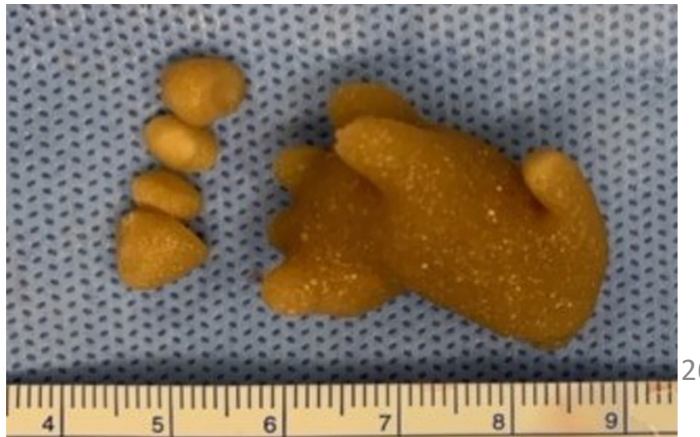
Cystinuria

- Mutations in genes encoding **proximal tubule** dibasic amino acid transporter which facilitates **reabsorption of cysteine**, ornithine, lysine, and arginine from tubular fluid.
- These amino acids generally have **good solubility**, cysteine can **dimerize** to form cystine that has poor water solubility at physiological urine pH and cause recurrent stones

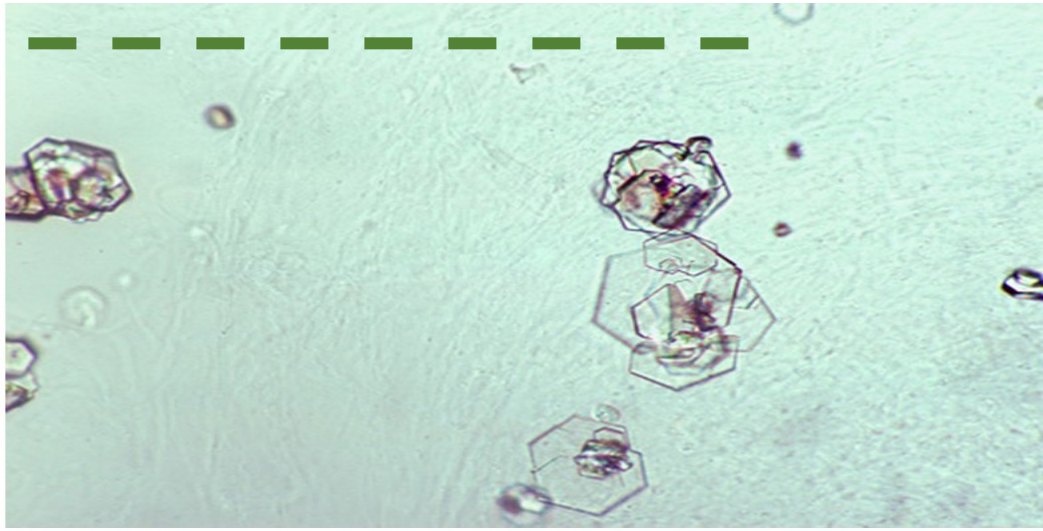
Cystinuria

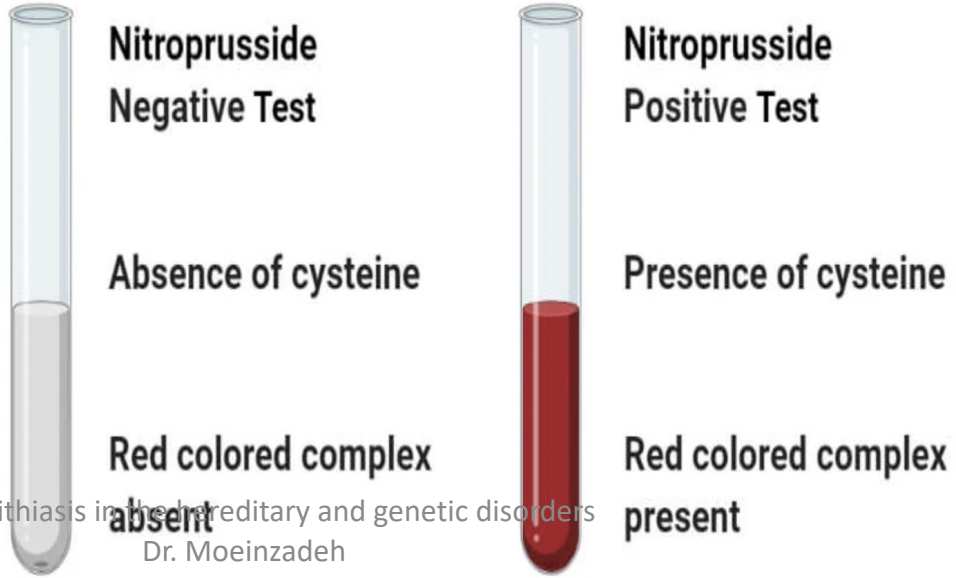
- In pediatrics: stone formation (average age 13y): 6-8% of stones.
- In adults: 1% of stones
- Clinical suspicious: FH of cystinuria
- Others clues:
  - Severe stone disease including recurrent or bilateral renal stones
  - Patients presenting with large staghorn calculi filling the collecting system and requiring surgery



Cystinuria diagnosis

- Microscopic urine sediment:
- Stone analysis
- For determining cystine hyperexcretion:
  - Sodium-nitroprusside test





Cystinuria diagnosis

- False-positive: homocystinuria, renal Fanconi syndrome, and patients taking ampicillin or sulfa-containing drugs.
- Positive results confirmation: quantitative chromatographic analysis of urine for cystine excretion.
- The gold standard test: 24-hour urine cystine excretion
  - In healthy subjects, daily urine cystine excretion is <30 mg.
  - Cystinuria patients typically have >300 mg/day of cystine excretion

Cystinuria diagnosis

- Genetic testing:
  - Atypical clinical presentation
  - Determining the mode of inheritance
  - Genetic counseling

Management of cystinuria

- **Conservative Management**
- ***Fluid intake***
- Cystine >250 to 300 mg/L is associated with higher supersaturation and greater risk of stone formation
- The goal of hyperhydration is to maintain urine output to keep cystine urinary concentrations less than that.
- **More than 4 L of urine/day** is recommended in adults.

Conservative Management

- ***Urine alkalinization***
- The goal pH to maintain cystine solubility is **7.5** or more.
- Potassium citrate: 10 - 30 mEq , 2 to 3 times per day.
- Gastrointestinal side effects were common with citrate supplements:
  - 12.3% of patients on K bicarbonate
  - 10.4% on K citrate
  - 2.6% on sodium bicarbonate

Conservative Management

- ***Diet***
- Low urinary sodium excretion reduces cystine excretion, and thus, a low salt diet of **< 2300 mg/d** is commonly prescribed.
- **Restricting animal protein** and **increasing plant-based protein** to meet daily protein intake of **0.8 g/kg** is recommended.

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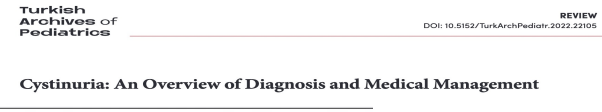
Cystinuria: An Overview of Diagnosis and Medical Management

Medications and Supplements Used in Cystinuria

Hydration: USG<1005 +

	Mechanism	Dose	Side Effects
Potassium citrate	Urine alkalinization	*Children*: 60–80 mEq/1.73 m²/day *Adults*: 60–80 mEq/day Frequency: 3–4 times per day	Gastrointestinal side effects. Hyperkalemia can be dose-limiting in patients with advanced CKD (consider sodium bicarbonate).
Penicillamine	Thiol drug, increases cystine solubility	*Children*: 20–30 mg/kg/day max dose 4000 mg/day *Adults*: 1–4 g/day Frequency: 3–4 times per day	Fever, rash, loss of taste, arthritis, leukopenia, aplastic anemia, gastrointestinal disturbance, membranous nephropathy with proteinuria, copper/zinc and pyridoxine deficiency
Tiopronin	Thiol drug, increases cystine solubility	*Children*: 15–40 mg/kg/day max dose 1500 mg/day *Adults*: 800–1500 mg/day Frequency: 3 times per day	Similar side effects as D-penicillamine with slightly less prevalence.
Captopril	Thiol drug, increases cystine solubility	*Children*: 1.5–6 mg/kg/day max dose 150 mg/day *Adults*: 75–150 mg/day Frequency: 3 times per day	Acute kidney injury, hyperkalemia, hypotension, cough
Alpha-lipoic acid	Increases cystine solubility	*Children*: 30 mg/kg/day max dose 1200 mg/day *Adults*: 1200 mg/day Frequency: 2 times per day	Nausea, vomiting, vertigo

30 mg/kg/d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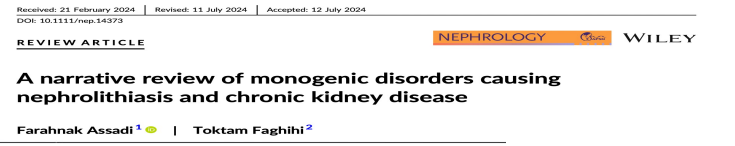
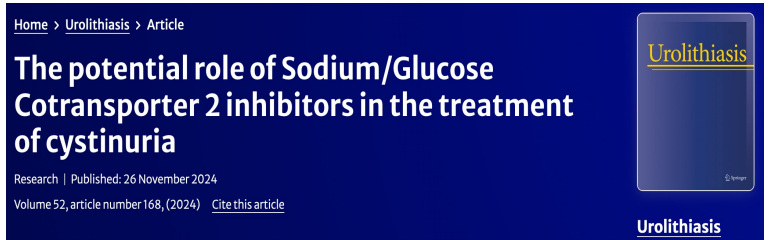

Received: 21 February 2024 | Revised: 11 July 2024 | Accepted: 12 July 2024
DOI: 10.1111/nep.14373
REVIEW ARTICLE
NEPHROLOGY WILEY
A narrative review of monogenic disorders causing nephrolithiasis and chronic kidney disease
Farahnak Assadi[1] | Toktam Faghihi[2]

Other new drugs

- **SGLT-2 inhibitors**: inhibit the formation of stones of other compositions, so they are currently also under investigation.
- Cystinuria treated with **dapagliflozin** experienced **fewer stone events** compared to their historical rates and decreased or stable stone growth.
- Recommendation: use in patients with **cystinuria** who also happen to have diabetes, albuminuria, or reduced glomerular filtration rates



Other new drugs

- ***Vasopressin Antagonists:***
- Blocking the antidiuretic hormone effect in the kidney, causes polyuria, which can theoretically reduce cystine concentration in the urine.
- Extreme thirst with tolvaptan treatment, which suggests that long-term treatment compliance might be problematic

MONITORING FOR TREATMENT ADEQUACY

- Cystine concentration: under solubility limit (243-250 mg/L) at urine pH 7.
- Urine pH is recommended to be kept around 7.5 to increase cystine solubility; however, clinicians should be aware of **increased calcium phosphate stone formation risk at high pH.**

MONITORING FOR TREATMENT ADEQUACY

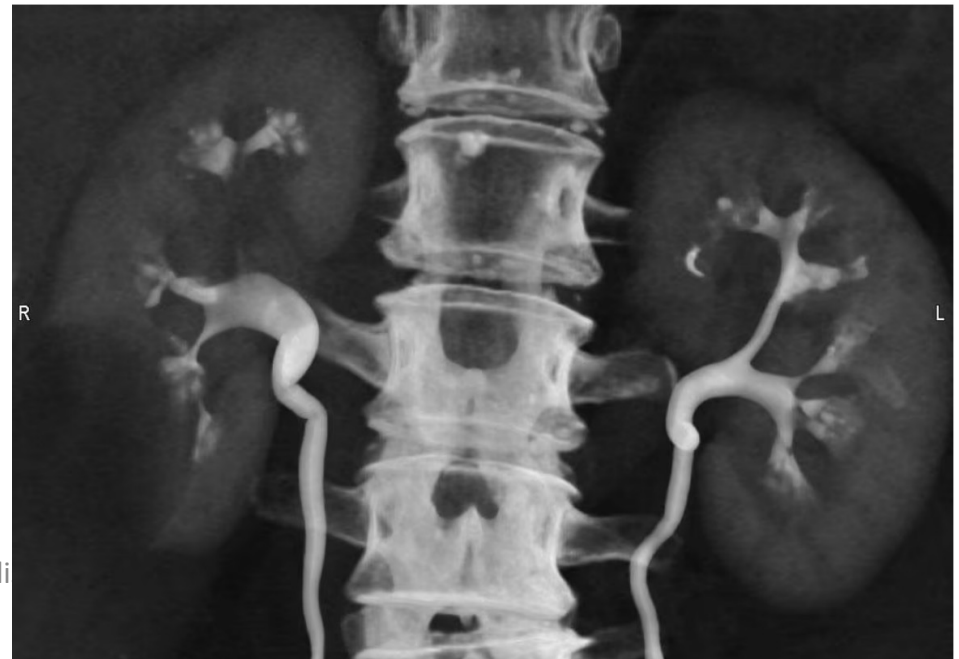
- In patients using **cystine-binding drugs**, cystine concentration and supersaturation become **unreliable** due to the chemical interactions between these drugs and cystine.
- Cystine capacity: marker of cystine solubility: not affected by cysteine-binding drugs, and positive capacity values suggest that urine is undersaturated

Cystinosis VS Cystinuria

- Cystinosis is a rare autosomal recessive lysosomal storage disorder
- Malfunctioning of the protein cystinosin, which is encoded by the *CTNS* gene.
- Accumulation of cystine within **cellular lysosomes**, leading to widespread organ involvement.
- Proximal tubulopathy: glycosuria, aminoaciduria, phosphaturia, bicarbonaturia, and other electrolyte losses.
- **Systemic Cysteamine Therapy**

Medullary sponge kidney

- Disruption to the normal ureteric bed-metanephric interface:
- Ectatic precalyceal papillary collecting ducts: nephrocalcinosis and nephrolithiasis, which may lead to recurrent urosepsis.
- Simple stones, ductal stones, ductal and inner medullary collecting duct plugs, pelvic stones



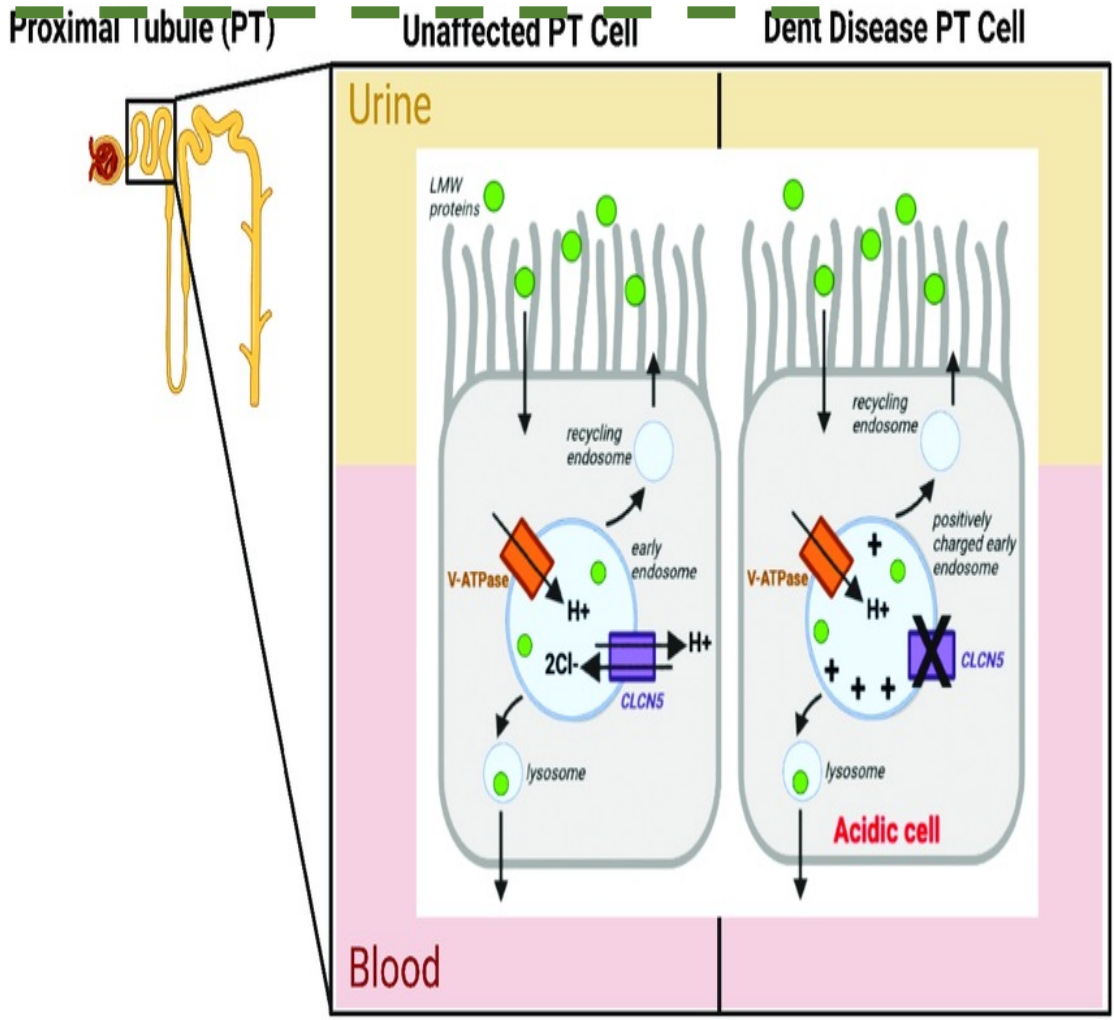
DENT DISEASE

- X-linked recessive disorder:
  - Renal Fanconi syndrome
  - Hypercalciuria
  - Nephrocalcinosis
  - Nephrolithiasis
  - ESRD out of keeping with the degree of nephrocalcinosis: 4^{th} to 5^{th} decade

genes
MDPI
Article
Genotype Phenotype Correlation in Dent Disease 2 and Review of the Literature: *OCRL* Gene Pleiotropism or Extreme Phenotypic Variability of Lowe Syndrome?

DENT DISEASE/ LOWE SYNDROME

- Dent-1: Mutations of the CLCN5 gene: encodes the chloride transporter ClC-5.
- Dent-2:Mutation in OCRL: Impaired reabsorption of filtered solutes
- LOWE SYNDROME: Dent disease + congenital cataracts and mental impairment.



genes

MDPI

Article

Genotype Phenotype Correlation in Dent Disease 2 and Review of the Literature: *OCRL* Gene Pleiotropism or Extreme Phenotypic Variability of Lowe Syndrome?

Pathophysiology of Hypercalciuria in Dent/Lowe

- Unknown mechanism
- Decreased chloride reabsorption in the proximal tubule: reduced calcium absorption in downstream nephron segments
- Disturbances in PTH, Vitamin D binding protein , …

Take Home Messages

- Primary hyperoxaluria treatment : Hydration +
  - vitamin B6: 5 mg/kg/day.
  - K-citrate dose: 0.1-0.15 mg/kg or 0.3-0.5 mmol/kg/day in three to four divided doses
- Cystinuria treatment: Hydration +
  - Potassium citrate: 10 - 30 mEq , 2 to 3 times per day.
  - Thiol based drugs