

METABOLIC EVALUATION AND MEDICAL TREATMENT OF UROLITHIASIS: "STONE TREES"

UCI

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Commercial Interest	Nature of Relevant Financial Relationship	
	What was received	For what role
Cook Urological	Speaker fees/royalties	Speaker's bureau / inventor
Applied Urology	Stock	Inventor / consultant
Boston Scientific Inc.	Research grant	Researcher
Karl Storz Inc.	Research grant	Researcher

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EVALUATION: BASIC “SERUM and URINE”

Electrolytes: r/o Renal tubular acidosis
(K, HCO_3^- , \downarrow Cl) \uparrow

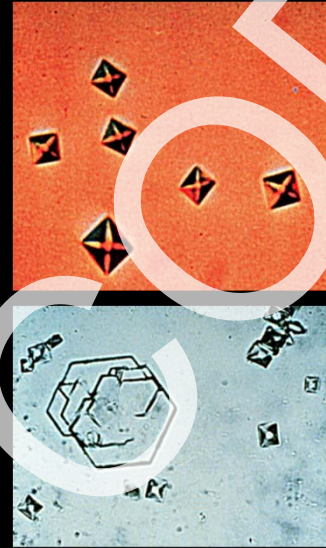
Calcium / Phos.: r/o
Hyperparathyroidism

(\uparrow Ca, \uparrow Cl, \downarrow Phos.)

Uric acid: (if urine pH < 6) r/o Gout

Glucose (type II diabetes)

Lipid profile (metabolic syndrome)



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METABOLIC STONE EVALUATION: “Yes”

1. Multiple calculi present
2. History of multiple stone episodes ($\geq 2/5$ years)
3. New stone formation
4. Stone growth
5. Positive family history

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METABOLIC EVALUATION: “Two 24 hr. URINE COLLECTIONS”

Think: internal standard, solute, promoter, inhibitor

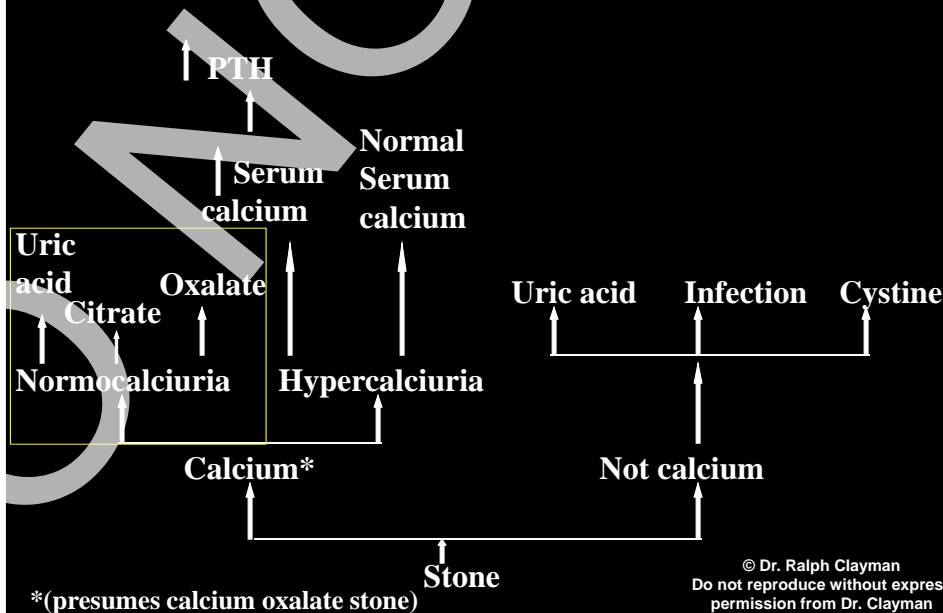
✓ One 24 hour urine collection: (suffices in 90% of cases)

- ✓ Internal standard: creatinine
- ✓ Solute: calcium, oxalate, uric acid
- ✓ Promoter: sodium, sulfate, monosodium urate
- ✓ Inhibitor: citrate

(Pak, C.: J. Urol. 165:378, 2001; Lotan, Y., Pearle, M., Pak, C., et al.: J. Urol. 172: 2275, 2004)

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STONE TREE: *DIAGNOSTIC “8”*



HYPERURICOSURIA: DIAGNOSIS (calcium oxalate stone)

R/O Gout

R/O Malignancy/Chemotherapy

U.A.(u): inc.

U.A.(s): NL or inc.

Urine pH: above 6

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HYPOCITRATURIA: DIAGNOSIS

R/O RTA (Type I; distal)

R/O Short gut syndrome

R/O Metabolic acidosis

Citrate (u): dec.

RTA: K⁺(s): dec.; HCO₃(s): dec.

Cl(s): inc.

Ca(u): NL; Urine pH: over 5.5

Check family members

± NH₄Cl load test

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HYPEROXALURIA: DIAGNOSIS

Primary – Type I Oxalate (u) > 90 mg

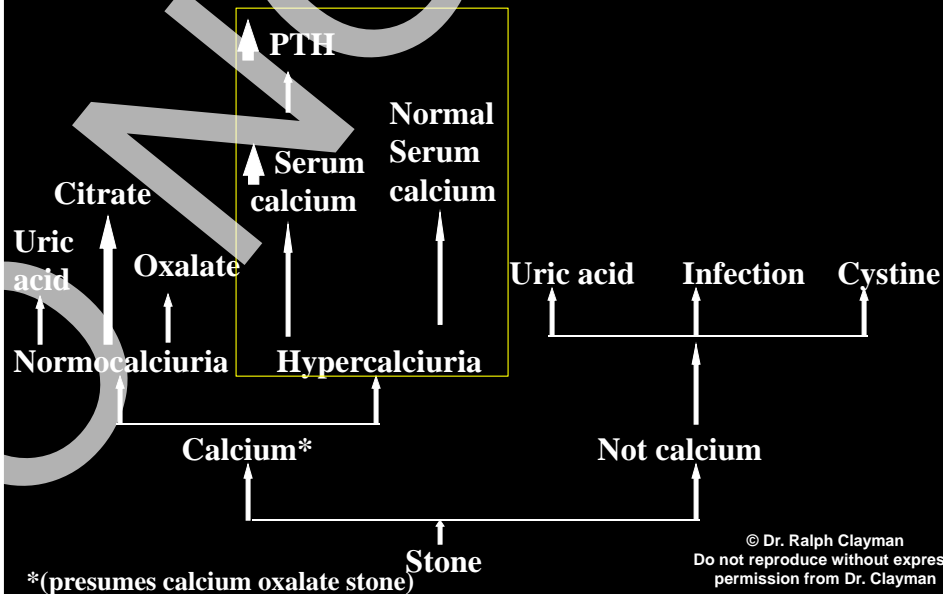
Enteric*: Bowel disease present
 or extensive small
 bowel resection

Idiopathic*: No bowel disease
 Dietary: high oxalate
 + low calcium diet

*(Oxalate levels: 45-80 mg/day)

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STONE TREE: *DIAGNOSTIC "8"*



HYPERCALCIURIA: HYPERPARATHYROIDISM

Ca(s): inc. (both total and ionized)

PO₄(s): dec.

Cl(s): inc. (Cl/PO₄: over 40)

PTH(s): inc.

Ca(u): inc. (> 400 mg/24 hrs.)

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HYPERCALCIURIA: NORMOCALCEMIA

Gut – Bone – Renal:

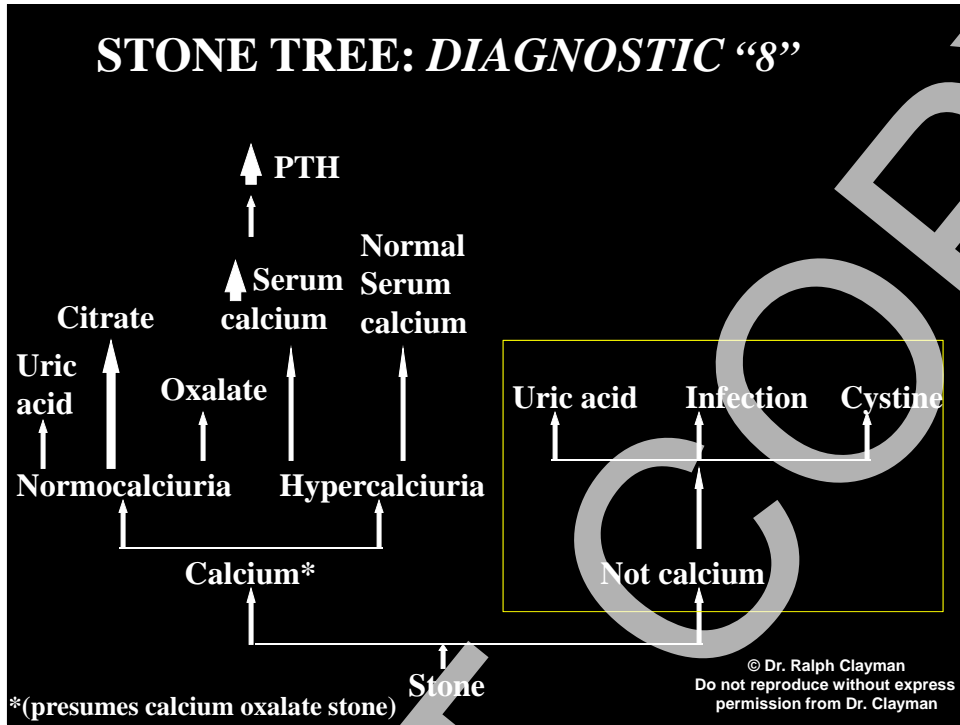
Ca(s): nl

PO₄(s): nl

PTH(s): nl (gut/bone) inc. (renal)

Ca(u): inc.

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HYPERURICOSURIA: DIAGNOSIS (uric acid stone)

Uric acid(s): NL or inc. (e.g. gout)

Uric acid(u): inc. or normal (e.g. gout)

Urine pH: (nearly) ALWAYS < 6

R/O gout or gouty diathesis (i.e. mildly inc. serum uric acid, pH < 5.5, normal uric acid excretion)

R/O chemotherapy/malignancy

R/O metabolic syndrome (diabetes/age > 40)

R/O protein gluttony (Adkins diet), chronic diarrhea
(Pak, C. Y. C. et al.: *Kidney International* 60: 757, 2001; Rodman, J. S.: *Urology* 60: 378, 2002)

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INFECTION STONES: DIAGNOSIS

**Urease splitting bacteria
(Proteus, Pseudomonas, Klebsiella)*
Urine pH: over 7**

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CYSTINURIA

Normal: < 60mg/24 hrs

Inheritance: Autosomal recessive

(heterozygote – 75-400 mg/24 hrs. vs. homozygote > 400 mg/24 hrs.)

Etiology: genes - SLC3A1 and SLC7A –defective rBAT protein precludes transport of dibasic amino acids (COLA) across intestinal and renal (proximal tubule) epithelial cells

Stone presentation: 14-28%: ≤ 3 yrs. of age

35-40%: 11 – 20 yrs. of age

Urine test: Cyanide nitroprusside positive if ≥ 250 mg/liter of urine on 24 hr. urine collection

(Chillaron, J., et al.: Nature Reviews Nephrol. 6: 424, 2010)

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METABOLIC EVALUATION: RESULTS (1,392 Patients)

Hypercalciuria:	37%
Hyperuricosuria:	28%
Hydroxaluria:	14%
Hypocitraturia:	44%
Low volume:	23%
RTA:	10%
Gouty diathesis:	20%
Enteric:	5%
Infection:	2.5%
Cystinuria:	2.8%
pPTH:	2.9%
No abnormality:	1.1%

(Pak, C. Y. C., Pearle, M. S., et al.: Am. J. Med. 115: 26-32, 2003)

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“WHAT” TO PRESCRIBE:

NOTHING!

ZERO!

ZILCH!

NADA!

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DRINK!

(96+ ounces/day)

Goal: Urine output = 2.5 l/d

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FLUIDS: WHAT TO DRINK?

Impact of type of fluids on stone formation: 3 cohort studies involving 194,095 participants among who over 8 years there were 4,462 stone incident cases.

	Risk
• Sugar sweetened noncolas	↑ 34% *
• Sugar sweetened cola	↑ 23% *
• Artificially sweetened noncola	Minimal risk
• Orange juice	↓ 12% *
• Caffeinated coffee	↓ 26% *
• Wine (red/white)	↓ 31% / 33% *
• Beer	↓ 41% *

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*²⁰ p < 0.05; Ferraro. P. Curhan, G. et al.: CJASN 8: May 15, 2013

UC Irvine Health

DIET: WHAT TO EAT?

- 1200 mg. calcium
(decreases oxalate levels)
- < 50 grams animal protein
(decreases uric acid, oxalate, and calcium excretion while increasing citrate levels)
- < 100 mmol (2.3 gram) NaCl
(decreases calcium excretion)

**Two fold decrease
in risk of recurrent stone disease**

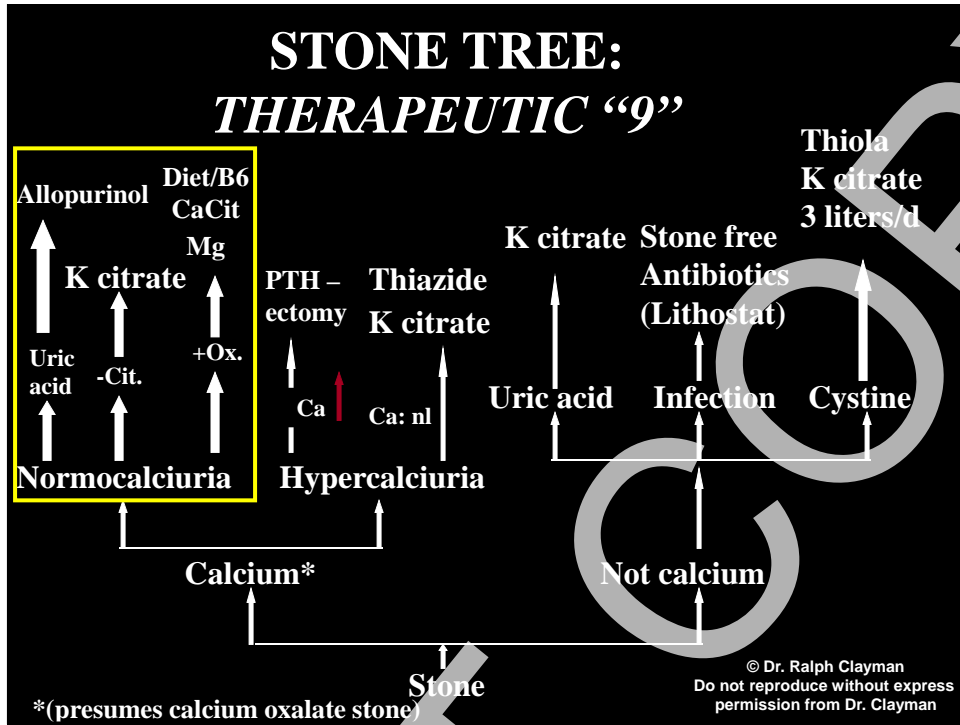
(Borghi, L. et al.: NEJM 10 (346): 77-84, 2002)

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WHEN DIET FAILS: WHAT TO PRESCRIBE?



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ALLOPURINOL

ACTION: Competitive (in low concentration) and noncompetitive (high concentration) inhibitor of xanthine oxidase

DOSAGE: 100 mg BID (maximum: 300 mg/d)

SIDE EFFECTS: skin rash, neutropenia, abnormal liver function tests, gastrointestinal symptoms, thrombocytopenia, cataract formation

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POTASSIUM CITRATE

(Urocit K (10 meq/tablet)/Cytra K (10 meq/crystal packet))

ACTION: increases urinary citrate levels:
increase urine pH

DOSAGE: 20 meq TID (maximum: 100 meq/day)

SIDE EFFECTS: hyperkalemia, GI complaints (33%)

COMPLIANCE RATE: $\leq 50\%$

COST (60 meq/d): \$600/month / \$87/month

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CITRATE: ALTERNATIVES

“60 meq/day”

- **Litholyte:** 10 meq/packet (5 meq K citrate, 2.5 meq Mg citrate, 2.5 meq Sodium bicarbonate) (50 mg. sodium/packet), and erythritol (an artificial sweetener): 60 meq/d costs \$96/month
- **Potassium citrate tablets (generic):** 10 tabs/d = 60 meq; \$11/month
- **Sodium bicarbonate tablets (650 mg):** 7.7 meq/tablet Cost: \$12/month
- **Kroger’s Low Calorie Orange Juice:** 1 liter/d inc. citrate by 178 mg/d and raised pH 0.74 in nonstone volunteers. Cost: \$67/month
- **Crystal light lemonade:** 1 liter/d inc. citrate by 156 mg/d and raised the pH 0.25 in nonstone volunteers. Cost: \$6/month
- **Baking soda:** sodium bicarbonate (1 teaspoon = 59 meq which is 1.2 gm sodium) Cost: \$0.34/month

(Large, T, Asplin J, Krambeck A: JE 2019; Pinheiro, V. et al.: Urol. 82: 33-37, 2013)

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PYRIDOXINE (VITAMIN B6)

- Action:** Promotes conversion of glyoxalate to glycine
Oxalate excretion falls by 30%
- Dosage:** 400 mg/day (max. 20 mg/kg/d)
- Side effects:** only with overdosage (2-6g/day): sensory neuropathy

(Balcke, P. et al.: P. Eur. Dial. Transp. Assoc. 20: 417, 1983)

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CALCIUM CITRATE (CITRACAL)

- Action:** Binds oxalate
Decreases calcium oxalate crystal formation
- Dosage:** 2-4 tablets/day (630 mg/2tab)
(Take with meals!)
- Side effects:** None noted

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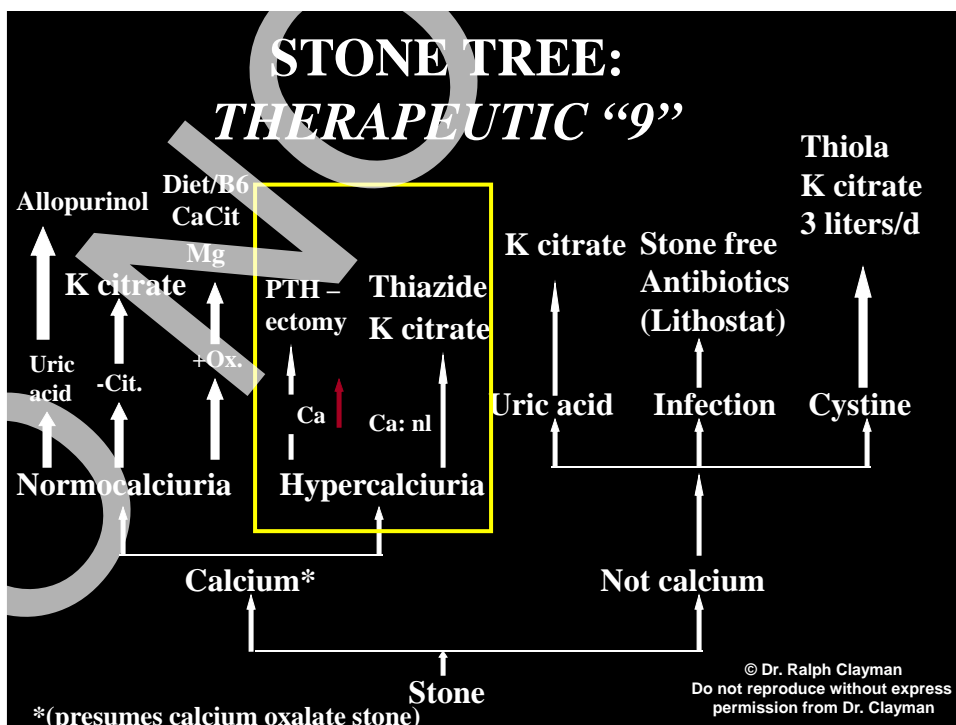
MAGNESIUM OXIDE (MagOx)

Action: Inhibits gut absorption of oxalate
Co-factor in decarboxylation of glyoxalate

Dosage: 400 mg/day (1 tablet)
(maximum: 800 mg/day)

Side Effects: laxative action

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THIAZIDE DIURETIC

ACTION: antihypertensive diuretic
 DCT: more calcium, less sodium reabsorption
 PCT: more calcium, more sodium reabsorption

DOSAGE: Chlorthalidone 12.5 mg p.o. QD
 (up to 25 mg p.o. QD)

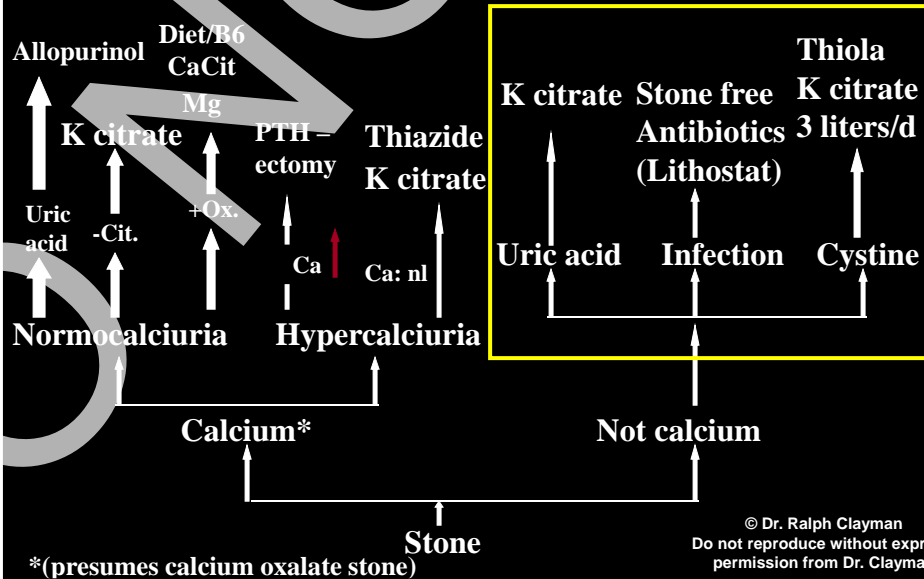
SIDE EFFECTS: symptomatic hypokalemia (3%),
 hyperglycemia, hyperuricemia, headache,
 lethargy, unmask normocalcemic
 hyperparathyroidism

COMPLIANCE RATE: 50-70%

(Huen, S. and Goldfarb, D.: J. Urol. 177: 1238, 2007)

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STONE TREE: THERAPEUTIC "9"



URIC ACID UROLITHIASIS: NUANCES OF ALKALINIZATION

1. **K citrate tablets: beware renal dysfunction / diarrhea**
2. **Sodium citrate: beware fluid overload / epitaxy (monosodium urate) / inc. calcium excretion**
3. **Consider once a day dose: goal pH 6.2-6.8; give 30-75 mEq – check pH 3 hrs. after dose.**

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STRUVITE CALCULI

Goals of Therapy:

1. **Stone free**
2. **Infection free**
(preventative antibiotics)

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ACETOHYDROXAMIC ACID*

- ACTION:** urease inhibitor
- DOSAGE:** 250 mg QID (maximum: 1.5 g/d)
- SIDE EFFECTS:** anemia: mild (16%) and severe (12%);
headache (11%); gastrointestinal upset (5%)
- CAVEAT:** AUA Guidelines Panel (2016) –AHA is a supportive measure only for patients who are not surgical candidates or if the fragments cannot be safely accessed/removed

*(Lithostat)

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CYSTINURIA: THERAPY

Goal: < 250 mg/L of cystine or cystine capacity > 100
(N.B.: Stone activity -38 vs. quiescent +48)*

1. Diet: high fluid (4.0 liters/day)
low sodium (\leq 150 mmol/day)
2. Alkalinization: potassium citrate:
pH 5: 190 mg/liter vs. pH 7: 400 mg/liter
3. Thiol: 50X Benefit
alpha mercaptoproprionyl glycine (tiopronin)
(10-30 mg/kg/d: 4 divided doses* - max. 1500 mg/d)
(plus Vit.B6: 50 mg qd)
(others: d penicillamine - poorly tolerated /
captopril – low effective amount)

(Chillaron, J., et al.: Nature Reviews Nephrol. 6: 424, 2010; *Friedlander, J, et al.: J. Urol. 199:495, 2018)

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ALPHA MERCAPTOPROPIONYL GLYCINE (THIOLA)

Action: thiol (SH) – disulfide exchange
2 Thiola + 1 Cystine = 2 Thiola-cysteine

Dose: 200 mg/QID

Side effects: mouth ulcers, nausea, hypogeusia,
leukopenia, anemia, nephrotic syndrome,
hematuria, proteinuria (25% stop therapy)

Effectiveness: Drops recurrent stone disease in half
(0.93 to 0.46 stones/pt/yr.)

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(Trinchieri, A., et al.: Archivio. Italiano di Urologia, Andrologia 76: 129, 2004)

AUA GUIDELINES: 2019 “MEDICAL MANAGEMENT of UROLITHIASIS”

- **Standard / Grade A evidence**
 - In patients on pharmacological therapy,
obtain periodic blood testing to assess
for adverse effects

(Pearle, M., Goldfarb, D., et al.: JU 192, 316, 2014 / reconfirmed 2019)

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AUA GUIDELINES: 2019

“MEDICAL MANAGEMENT of UROLITHIASIS”

- **Standard / Grade B evidence – 7 points**
 - In high risk, recurrent, or interested first time stone formers perform additional metabolic testing (24 hour urine collection)
 - Fluid intake (*of 96 ounces/d*) to achieve 2.5 liters/d. of urine
 - For calcium stone formers: limit sodium intake (2.3 gm/d) and normal calcium intake (1-1.2gm/d)
 - In calcium stone formers:
 - if hypercalciuria – give a thiazide
 - if hypocitraturia – give K citrate
 - if hyperuricosuric – give allopurinol.
 - if no abnormalities - give a thiazide and K citrate

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(Pearle, M., Goldfarb, D., et al.: JU 192: 316, 2014 / reconfirmed 2019)

CONCLUSIONS: DIAGNOSTIC

- Serum studies (BMP/calcium/uric acid/lipid screen/glucose) and urinalysis (+/- culture) with stone analysis suffice in the majority of patients. In recurrent calcium oxalate stone formers, consider bone density test too.
- 24 hour urine collection(s) is justifiable only in patients with 2 or more stone recurrences or presentation with multiple stones or young age with + family history

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CONCLUSIONS: THERAPEUTIC

- **Drink and diet alone work!**
“ONE OF THE FIRST DUTIES OF THE PHYSICIAN IS TO EDUCATE THE MASSESS NOT TO TAKE MEDICINE.” Osler
- **For those who develop a second stone select option a: citrate therapy or 24 hr. urine collection(s) and directed therapy.**
- **If select citrate therapy and there is a third stone episode, proceed to 24 hr. urine collection(s) and directed therapy.**

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UROLITHIASIS: 2020

An Oslerian view:

“Diseases that harm
require
treatments
that
harm less.”



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