MEDICAL MANAGEMENT OF KIDNEY STONES

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BRRH Grand Rounds
October 13th, 2015

Conflicts of Interest

- None

Objectives

- Epidemiology
- Acute Renal Colic
- Types of Stones
- Risk factors for Stone Formation
- Treatment for Stone Prevention
- Show obligatory cute picture of kids

Annals 11/2014

- "Dietary and Pharmacologic Management to Prevent Recurrent Nephrolithiasis in Adults: A Clinical Practice Guideline from the ACP"

- Rec #1: "…increased fluid intake throughout the day to achieve at least 2L of urine per day…"

- Rec #2: "…pharmacologic monotherapy with a thiazide diuretic, citrate, or allopurinol to prevent recurrent nephrolithiasis in patients with active disease in which increased fluid intake fails to reduce the formation of stones…"

Rebuke

- Dr. David Goldfarb
  - Nephrologist- NYU
  - Kidney stone expert
  - American Urological Association guidelines

  - "…I would not distribute the paper to a resident or fellow if instruction in the care of patients were the goal."

Epidemiology

- 2 million outpatient visits/ year in US (2000)
- $2-5 billion in annual expenditures

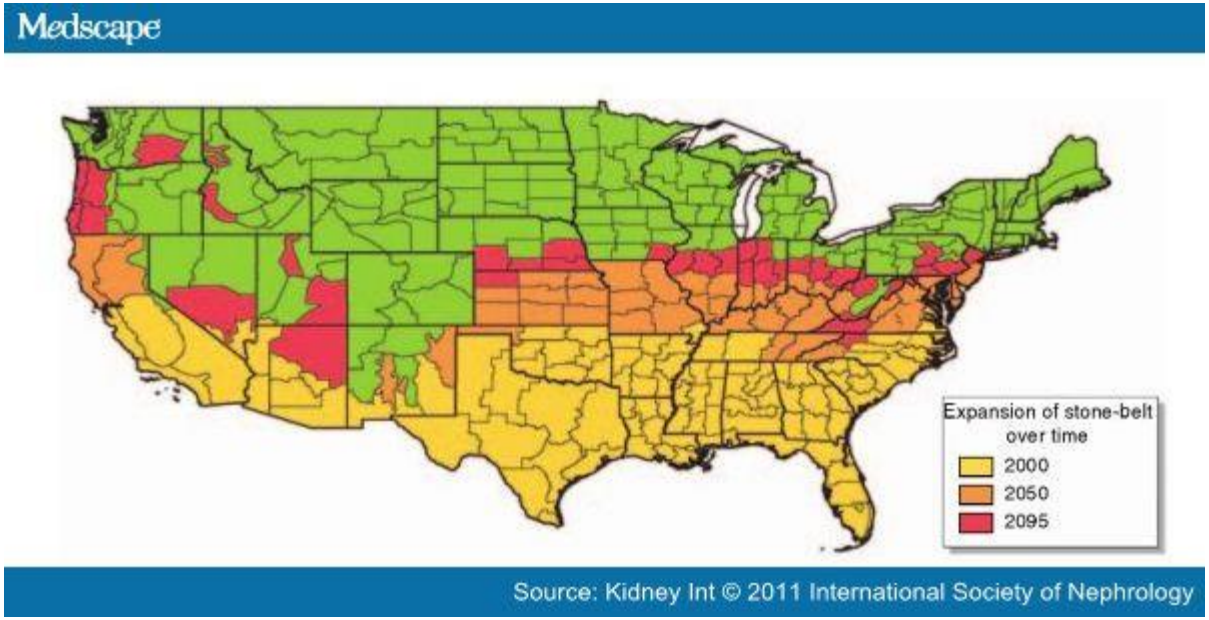
- Stone formation by age 70:
  - 16% of men
  - 8% of women

- Prevalence increasing in US
  - 3.8% (1970s) -> 7.4% (2000s)

Scales CD Eur Urol. 2012

Demographic Risk Factors

- M > F
  - Ratio decreasing
- Caucasians
- "Stone Belt"
- Obesity



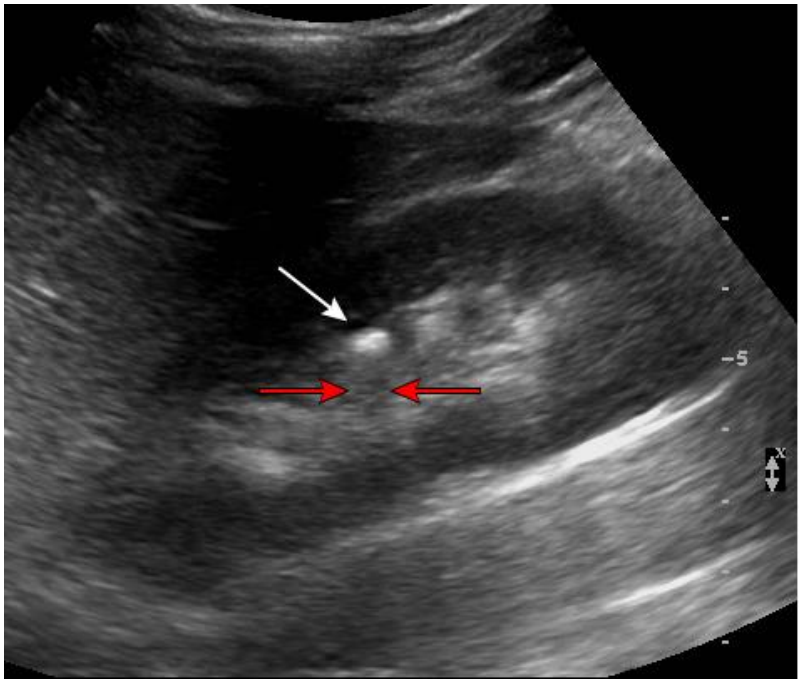
Scales CD Eur Urol. 2012

Case

- 35M overweight presented to the ED with 36 hours of nausea, vomiting, gross hematuria, and L flank pain
- Exam: appears uncomfortable, +L CVA tenderness
- Labs: Electrolytes normal, UA >180 RBC
- ***Next step: Imaging, but which type?***

Imaging

- CT (non-contrast) OR Renal US



Imaging

- CT
  - PROS:
    - More specific for stone detection (~100%)
    - Alternate diagnoses
    - Better to assess ureteral dilation
    - Stone composition identification?
  - CONS:
    - Radiation

- US
  - PROS:
    - No radiation
    - Can assess ureteral dilation
    - Can identify stones missed by KUB
  - CONS:
    - Can miss small or ureteral stones
    - Can miss alternate diagnoses

Imaging comparison

- RCT- 2759 ED patients presenting with likely stone sx to:
  - 1. US (read by ED physician)
  - 2. US (read by radiologist)
  - 3. CT

- CT:
  - More radiation (2x)
  - More sensitive (88%)

- US:
  - More time in ED (rad)
  - Less sensitive (54-57%)
  - 41% of pts -> CT anyways

  - No difference in "missed" diagnoses

Smith et al. NEJM 2014

KUB

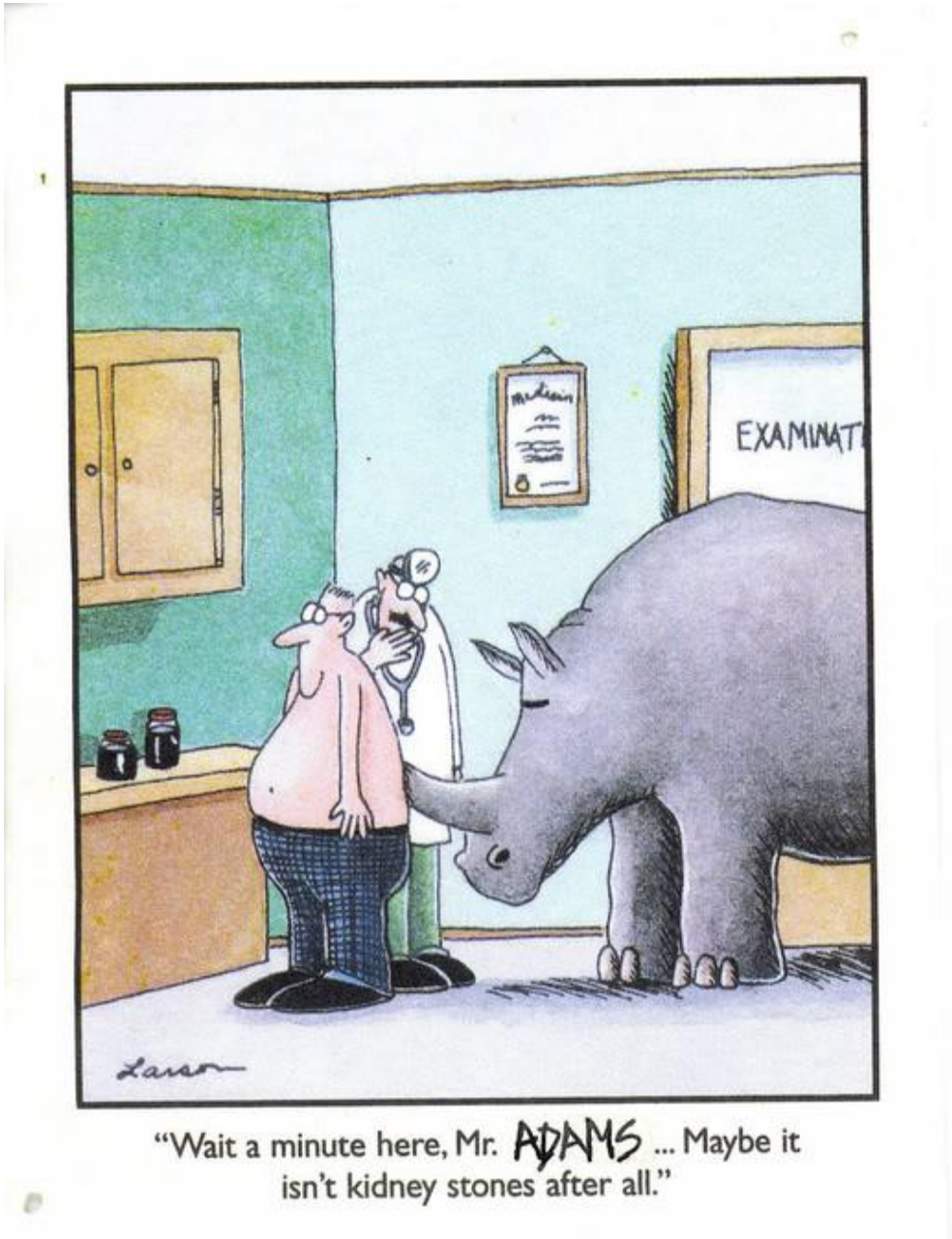
- Better for follow-up
- Misses uric acid stones
- Misses small stones
- Misses obstruction

IVP

- Identifies obstruction
- Contrast load
- Useful in medullary sponge kidney

Renal Colic

- Pain
  - Paroxysmal 20-60 minute "waves"
  - May radiate or migrate
- Hematuria (70%)
  - Gross or microscopic
- N/V
- Dysuria + urgency
  - Distal ureter/UVJ
- ***DDX is broad…***



Medical Expulsive Therapy (MET)

- Hydration
- Analgesia
- Meds to facilitate stone passage

- Urologist immediately if…
  - Sepsis
  - Stone > 10mm
  - AKI and/or anuria

Hydration

- 43 pts with renal colic
  - Arm 1- 1L NS/hr x 2 hours (n=20)
  - Arm 2- 20mL NS/hr (n=23)

- No difference:
  - Stone size
  - Pain + med requirements
  - Stone passage rates

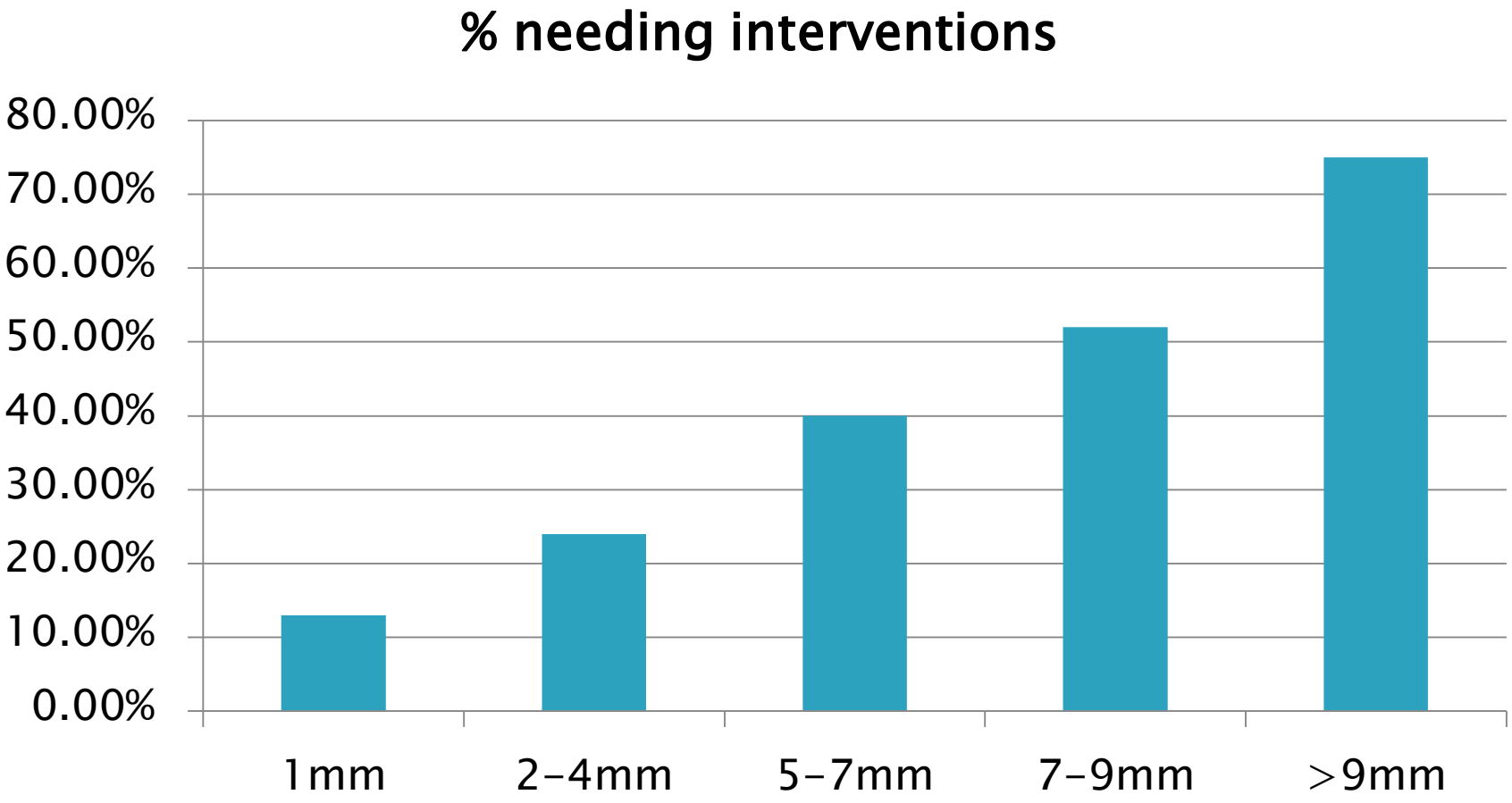
Springhart, et al. J Endo Urology 2006

Analgesia

- NSAIDS
  - Decrease ureteral tone
  - Better choice for malingering
  - Less nausea/vomiting
  - Not ideal if AKI, volume depleted
- OPIATES
  - Better pain relief than NSAIDs after 10 min
  - No difference after 20-30 min
- COMBINATION
  - Better than either agent alone after 40 min

Cordel, WH. Ann Emer Med 1994 / Safdar et al. Ann Emer Med 2006

Will my stone pass?



Coll AJR 2002

MET

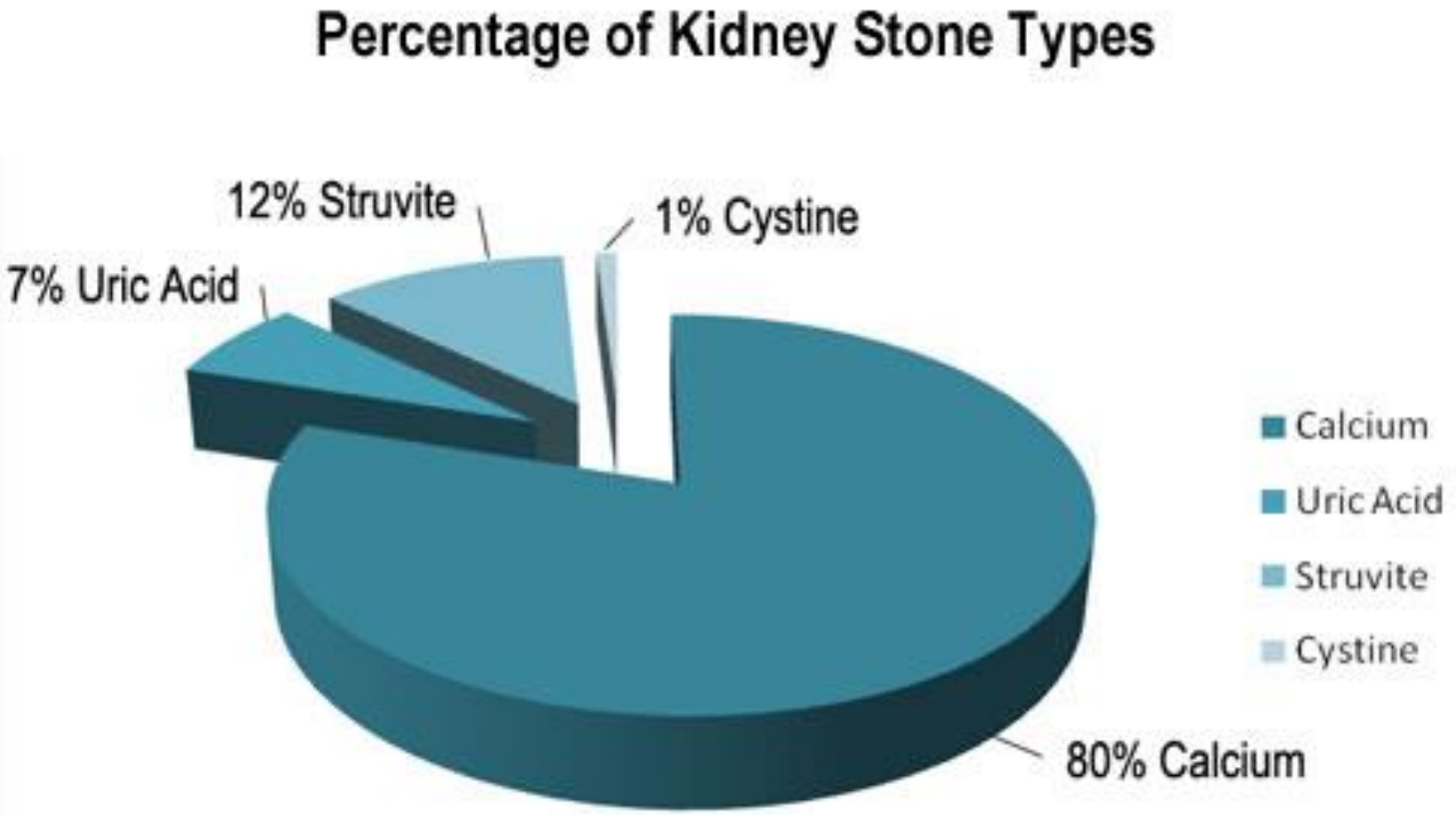
- Alpha Blockers
  - Tamsulosin (Flomax), Doxazosin
  - Decrease intraureteral pressure
- Calcium Channel Blockers
  - Nifedipine
  - Relaxes ureteral smooth muscle
- Multiple meta-analyses:
  - More likely to pass stones (65%; NNT = 4!!!)
  - Quicker expulsion
  - Less pain
  - Less hospitalizations

Hollingsworth. Lancet. 2006.

Case

- Pt hydrated and given Toradol for pain relief and sent home with Rx for Flomax 0.4mg/d.
- Passes stone into strainer 4 days later
- Now what?

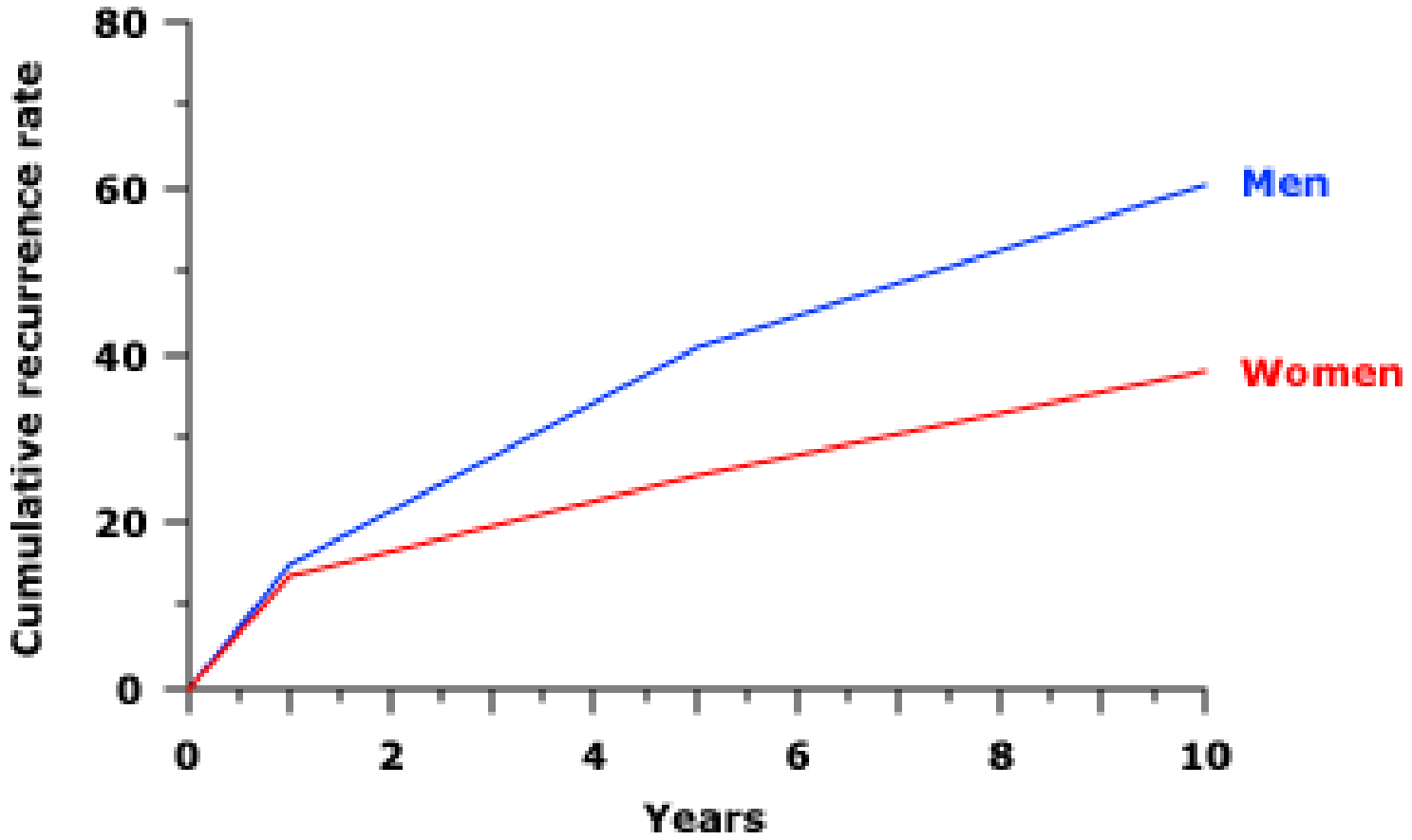
Stone Analysis/Composition



Oxalate OR Phosphate

Kidneystonetreatmentreviews.com.

Risk of stone recurrence



Uribarri. Annals Int Med. 1989.

Further workup

- After first stone:
  - Everyone gets H&P, review of imaging
  - Limited evaluation
    - Chem
  - Complete evaluation (Parks, Coe. KI. 1994)
    - Chem, UA, 24hr urine
    - Multiple stones, recurrent, peds
  - "Targeted evaluation"
    - Same as complete if high risk of recurrence

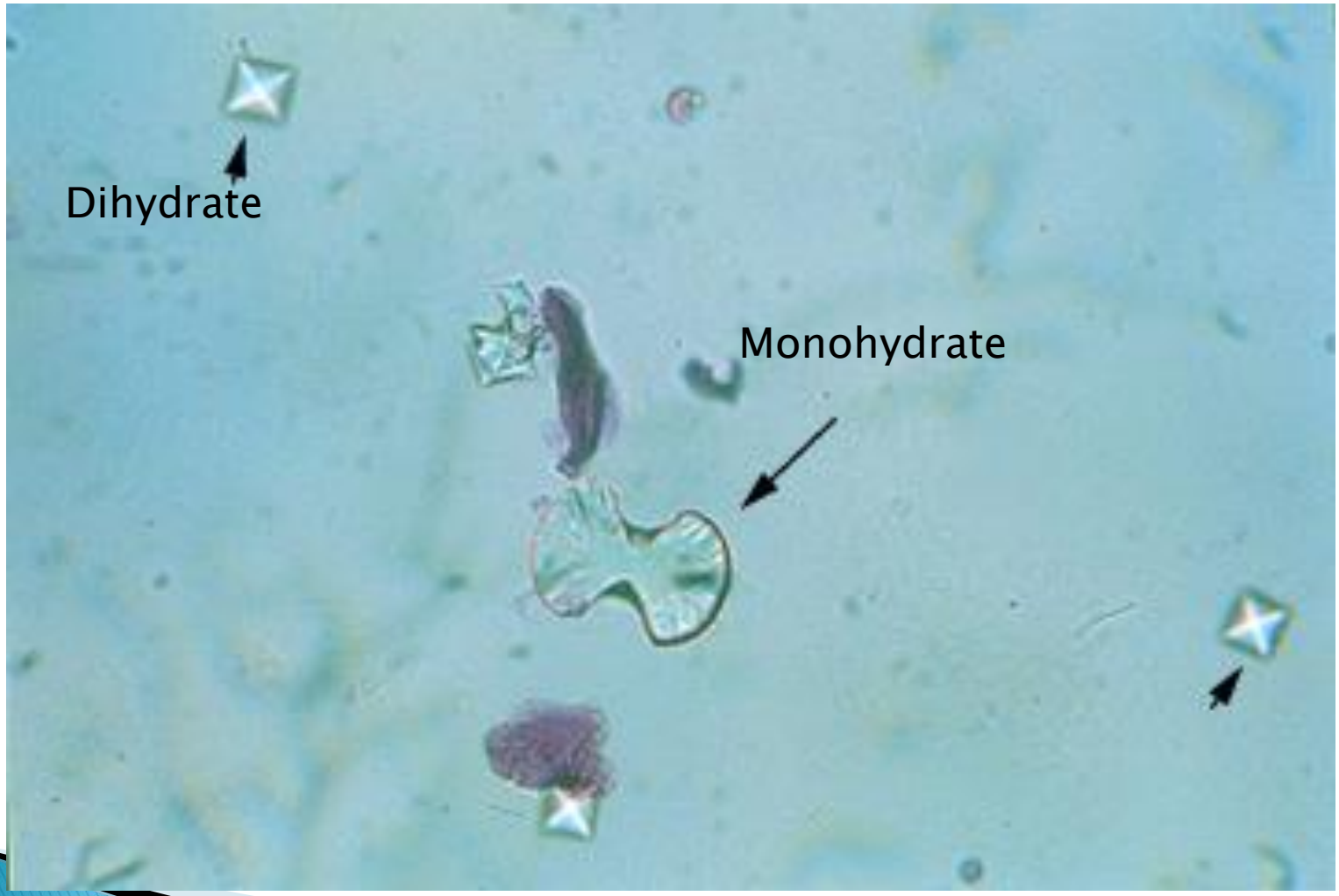
History

- Medical History
  - OP, Bowel dz, Gout, UTI, Granulomatous dz
- Family History
  - Increased RR 2.5x with +FH
- Medications, including vitamins and supplements
  - Topamax, Sulfa, HAART, Vit C, Abx
- Diet
  - Salt, Oxalate, Calcium, Protein

Labs

- Calcium + Phos
  - PTH?
- Bicarbonate
- Uric Acid
- Urinalysis
  - pH
  - Sediment → crystals

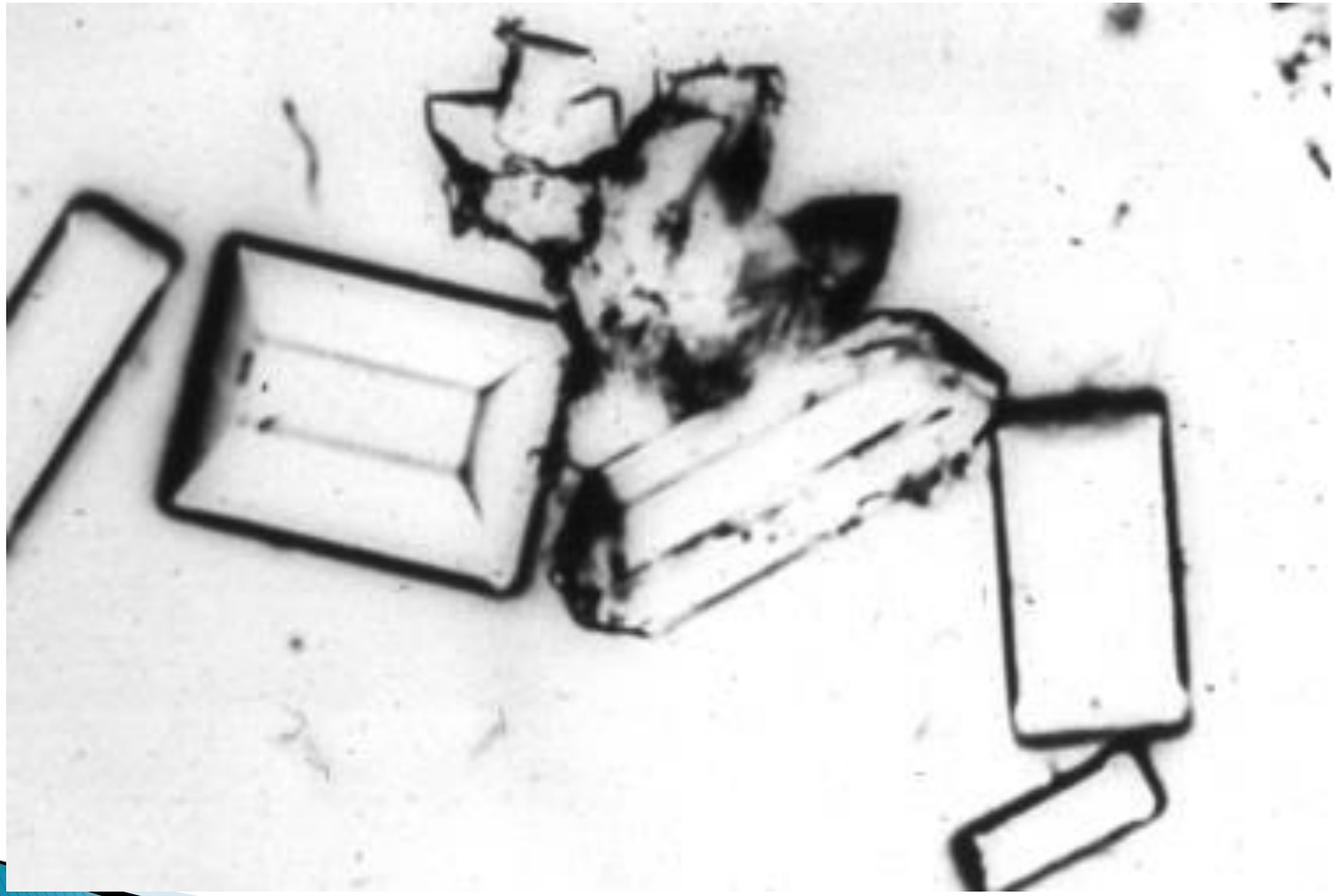
Calcium Oxalate



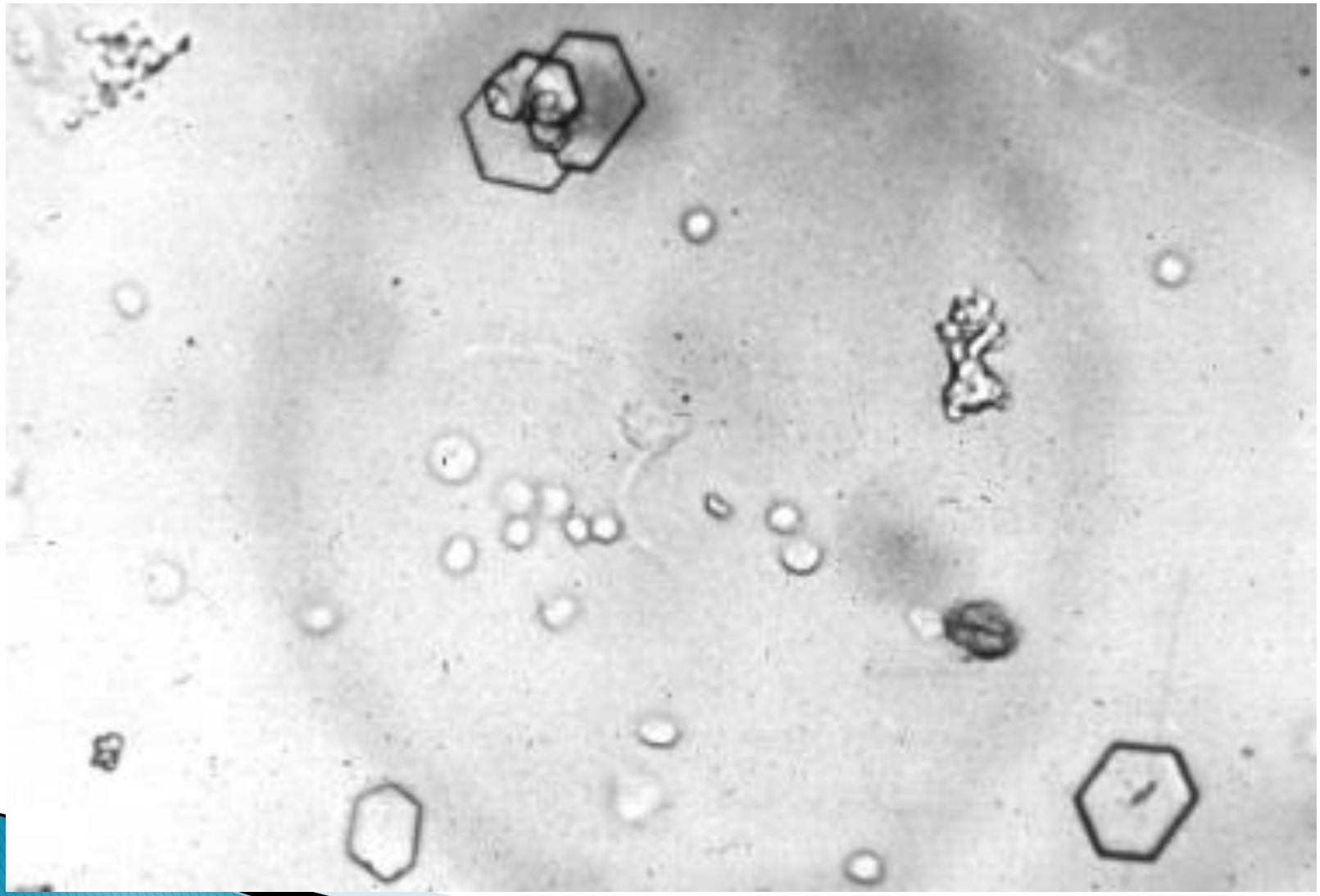
Calcium Phosphate

Uric Acid

Struvite (Triple Phosphate)

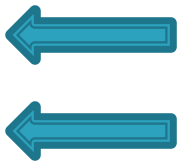


Cystine



24 Hour Urine Collection

	"Normal" (male)	"Normal" (female)
Volume	>2L	>2L
pH	5-8	5-8
Sodium	<150 meq	<150 meq
Citrate	>320 mg	>320mg
Calcium	<300 mg	<250 mg
Uric Acid	<800 mg	<750 mg
Oxalate	<45 mg	<45 mg
Creatinine	20-25 mg/kg	15-20 mg/kg



Curhan. KI. 2001

24 Hour Urine Collection

- "Normal" values? Or actually a spectrum?

Variable	NHS I					NHS II					HPFS			
	Cases	Control	RR	95% CI		Cases	Control	RR	95% CI		Cases	Control	RR	95% CI
Calcium *mg/day*														
<150	83	41	1.00	—		39	13	1.00	—		68	36	1.00	—
150–199	53	19	1.45	0.73–2.89		36	8	2.05	0.67–6.25		58	23	1.23	0.63–2.37
200–249	62	12	3.06	1.38–6.79		30	4	4.68	1.19–18.41		65	26	1.31	0.67–2.56
250–299	34	12	1.47	0.63–3.45		28	2	12.66	1.76–91.24		50	9	2.56	1.09–6.02
300–349	29	7	2.21	0.81–6.05	300+	36	3	14.62	2.66–80.26		35	5	3.77	1.26–11.26
350+	36	8	2.58	0.93–7.20							48	11	2.44	0.96–6.18
P, trend				0.03					0.008					0.006

Curhan. KI. 2001

Urine Volume

- Goal: > 2L/day
  - Proven in prospective trials

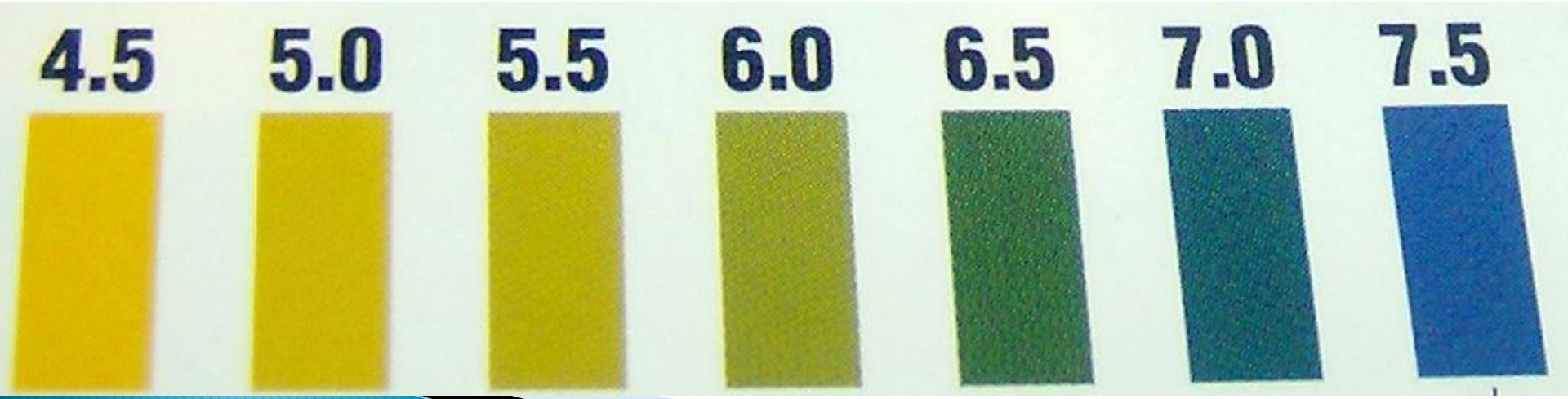
- Increased urine flow rate
- Decreased urine solute concentration

- Type of fluid: Generally everything okay
  - Avoid: soda, ?grapefruit juice
  - Okay!: coffee, tea, modest EtOH

Borghi, J Uro, 1996

Urine pH

- Acidic urine: uric acid stones
- Alkaline urine: calcium phosphate stones
  Struvite stones
- Calcium Oxalate stones form at variable pH



Hypercalciuria

- "Abnormal" > 250-300mg/day
- 50% of stone formers

- Three classes:
  - **Absorptive**: GI
  - **Resorptive**: Bone
  - **Renal**

Idiopathic Hypercalciuria

- Most common type
- Normal serum calcium, phos, vitD, PTH

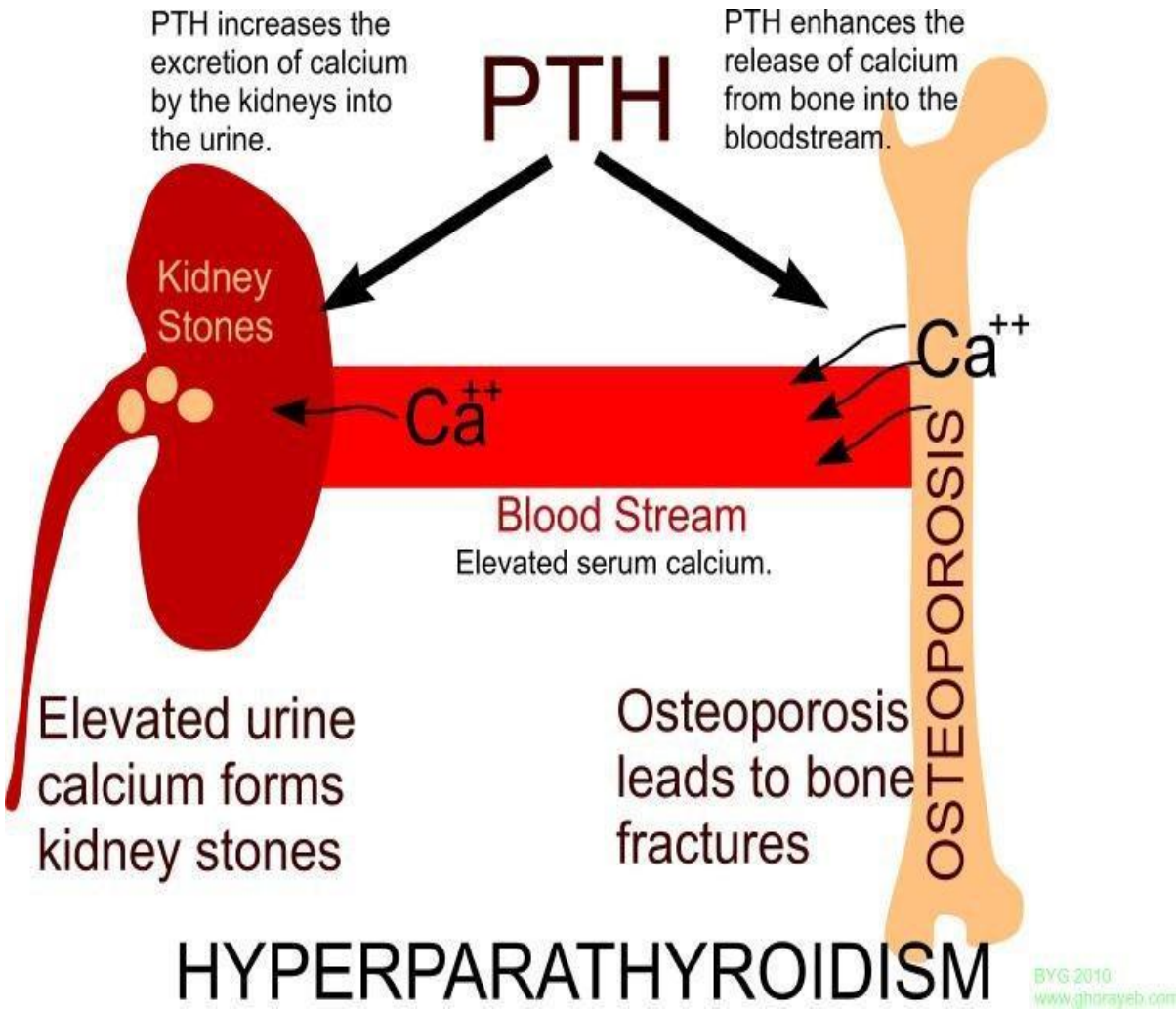
- Inherited?

- Proposed Mechanism: renal phos wasting → increased synthesis of 1,25 OH Vitamin D → increased calcium absorption/resorption → hypercalciuria

Hyperparathyroidism

- 15-20% form stones
- Usually CaOx
- Tx: PTx

- RR stones normalized 10 yrs post-op



Mollerup BJM 2002

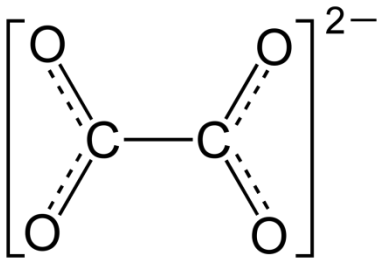
RTA

- Type 1- Distal
  - Impaired urinary acidification (elevated urine pH)
- Acidosis → low urine citrate
  - Decreased filtration
  - Increased reabsorption
- Hypercalciuria
  - Caused by RTA (inherited)
  - The cause of RTA (inherited -> nephrocalcinosis)

Hypocitraturia

- Citrate = "stone blocker"
- Binds calcium in tubular lumen → soluble complex
- Inhibits crystal agglomeration
- Causes: RTA, diarrhea, high protein diet, carbonic anhydrase inhibitors

Hyperoxaluria



- Higher risk of calcium oxalate stones as urinary oxalate rises > 25
- Exogenous- found naturally in plants
- Endogenous- primary hyperoxaluria
- Enteric- short gut

Hyperoxaluria

NHS1	Oxalate, mg			
	<20	100	63	1.00 (Ref.)
	20–24	171	105	1.15 (0.75–1.77)
	25–29	224	99	1.59 (1.03–2.46)
	30–39	278	93	2.51 (1.59–3.96)
	40+	125	43	2.36 (1.35–4.13)
	P, trend			<0.001
NHS2	Oxalate, mg			
	<20	116	75	1.00 (Ref.)
	20–24	167	70	1.78 (1.14–2.80)
	25–29	158	64	1.81 (1.13–2.90)
	30–39	173	65	2.09 (1.27–3.43)
	40+	89	22	3.58 (1.85–6.94)
	P, trend			<0.001
HPFS	Oxalate, mg			
	<25	36	51	1.00 (Ref.)
	25–29	72	45	2.35 (1.28–4.32)
	30–39	203	146	1.90 (1.12–3.22)
	40–49	178	92	2.67 (1.52–4.70)
	50+	147	80	3.22 (1.72–6.05)
	P, trend			0.005

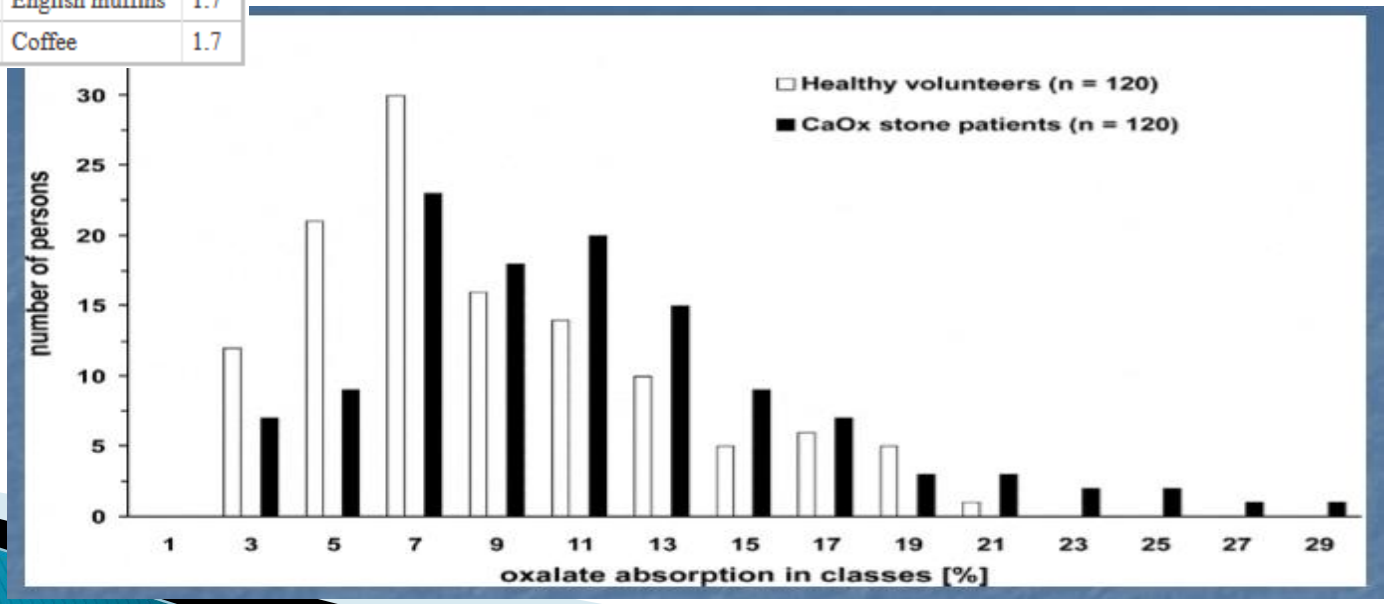
Curhan. KI. 2008

Exogenous hyperoxaluria

- Diet:

HPFS		NHS I		NHS II	
Food	%	Food	%	Food	%
Cooked spinach	23.1	Cooked spinach	25.8	Cooked spinach	22.0
Raw spinach	17.3	Raw spinach	18.4	Raw spinach	20.3
Potatoes (whole)	10.2	Potatoes (whole)	11.1	Potatoes (whole)	9.9
Cold cereal	4.4	Cold cereal	4.3	Cold cereal	3.8
Oranges	2.9	Oranges	2.5	French fries	2.5
French fries	1.9	Coffee	1.7	Oranges	2.0
Mixed nuts[b]	1.7	Cooked carrots	1.7	Pasta	2.0
Navy beans (canned)	1.7	Tea	1.6	Pasta sauce[d]	1.9
Cookies[c]	1.6	Cookies[c]	1.5	English muffins	1.7
Peanuts	1.6	Pasta sauce[d]	1.4	Coffee	1.7

- Normal < 5% absorption
- CaOx stone formers absorb 20% more dietary oxalate (Voss J.Uro. 2006)

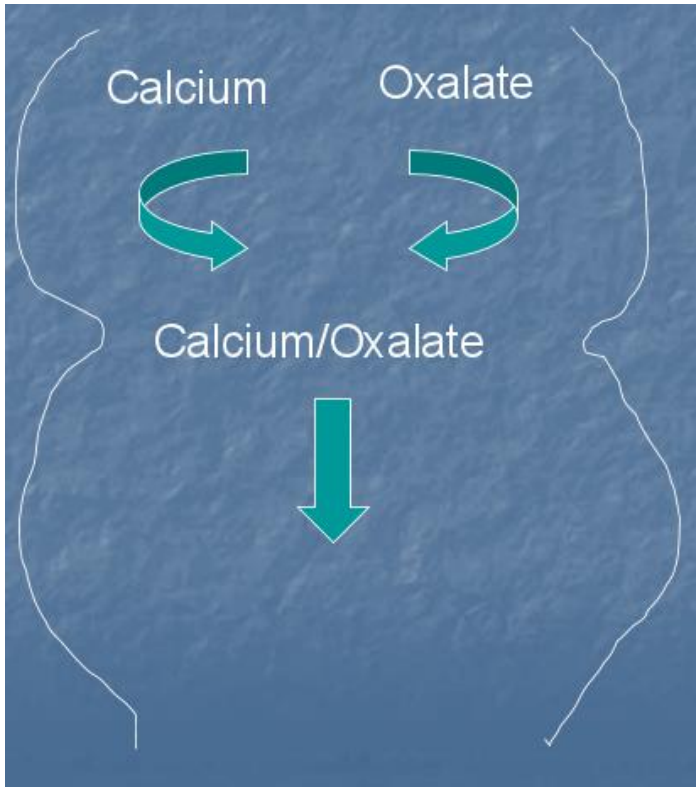


Endogenous Hyperoxaluria

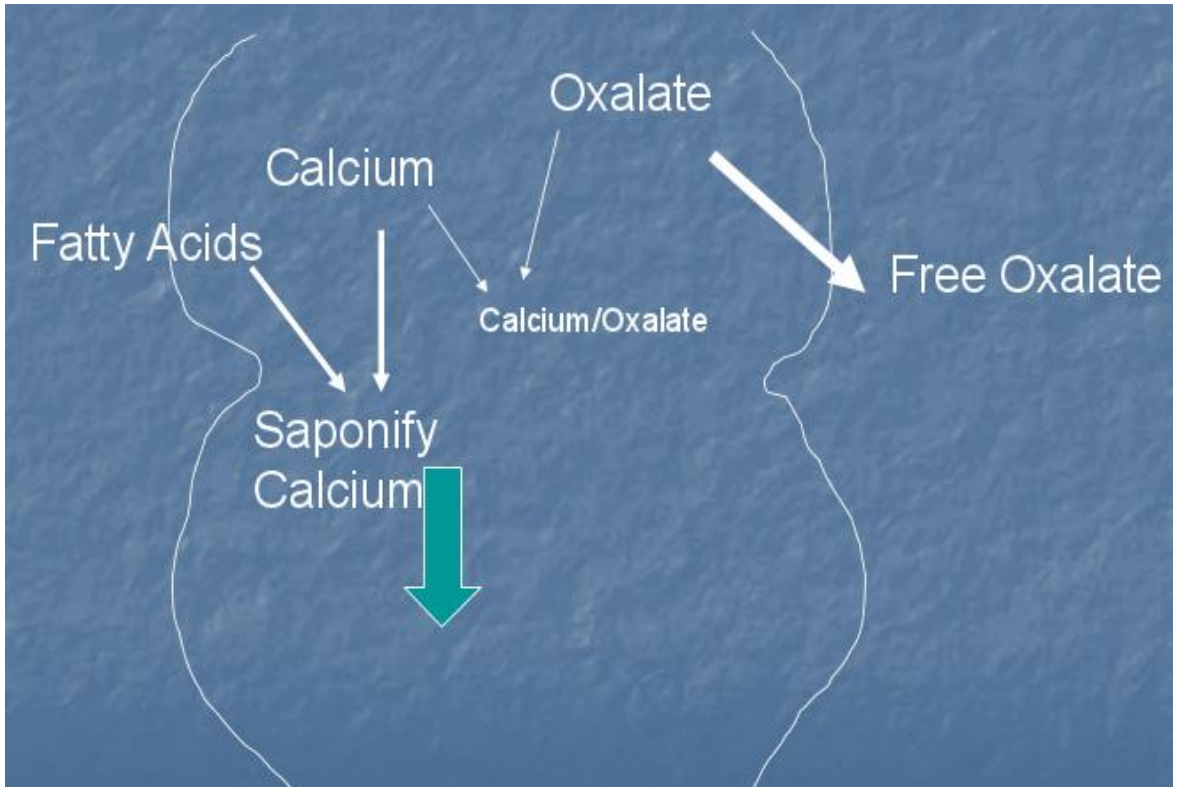
- PH 1/II
- Rare inherited condition
- Urinary Oxalate > 100-200mg/day
- Deficiency of enzyme in liver
- Widespread CaOx deposition
- Tx: liver transplant

Enteric Hyperoxaluria

- Normal



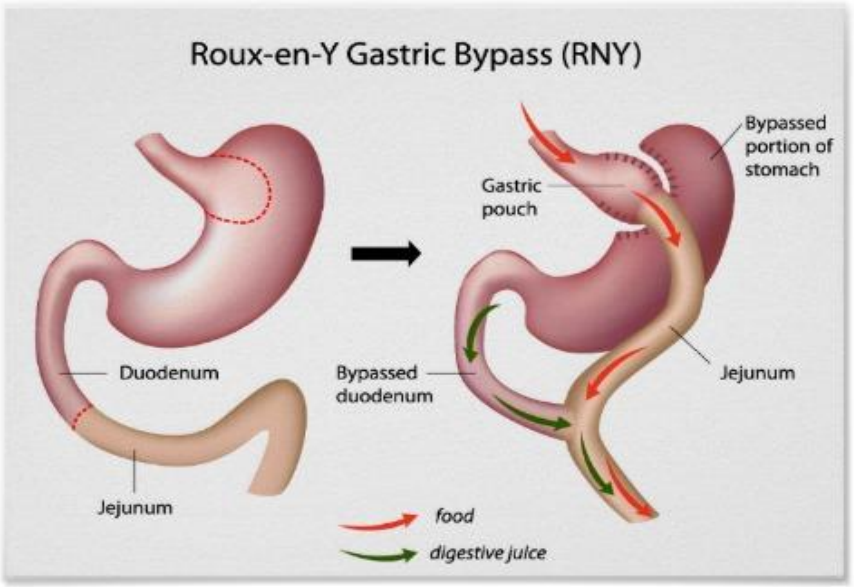
Fat malabsorption



Gastric Bypass, Diarrhea, Small bowel disease, Pancreatic exocrine insufficiency
increased colonic permeability

Courtesy: Dr Denu-Ciocca, UNC-KC

Gastric Bypass



- Jejueunal-Ileal bypass
  - Abandoned in late 1970s
- Roux-en-Y
  - Higher oxalate excretion (83mg) vs controls (30s mg)
- Gastric Banding/Sleeve
  - Lower oxalate excretion (35mg vs 61mg/day RYGB)

Asplin/Coe J Urology 2007. Semins. Urology, 2010.

Gastric Bypass (Roux-en-Y)

	Preop Median (Q1, Q3)	Postop Median (Q1, Q3)	Change	P value
Calcium (mg/d)	176 (128,232)	135 (70, 171)	63	< 0.0001
Oxalate (mg/d)	32 (25, 41)	40 (31,50)	8	0.01
Uric Acid (mg/d)	583 (411, 779)	412 (308, 477)	271	< 0.0001
Citrate (mg/day)	675 (367, 1,071)	456 (302, 824)	- 183	0.0006
Total volume (l/d)	1.8 (1.08)	1.44 (0.86, 1.80)	- 0.46	0.002
Sodium (mEq/d)	188 (150, 295)	143 (100, 175)	73	<0.0001
CaOx (SS)	1.27 (0.79, 1.92)	2.33 (1.34, 3.58)	0.76	<0.001
Uric acid (SS)	1.52 (0.68, 2.77)	2.14 (1.03, 4.04)	0.32	0.2
pH	6.03 (5.59, 6.27)	5.75 (5.4, 6.18)	- 0.10	0.18

Park. J Uro. 2009

Hyperuricosuria

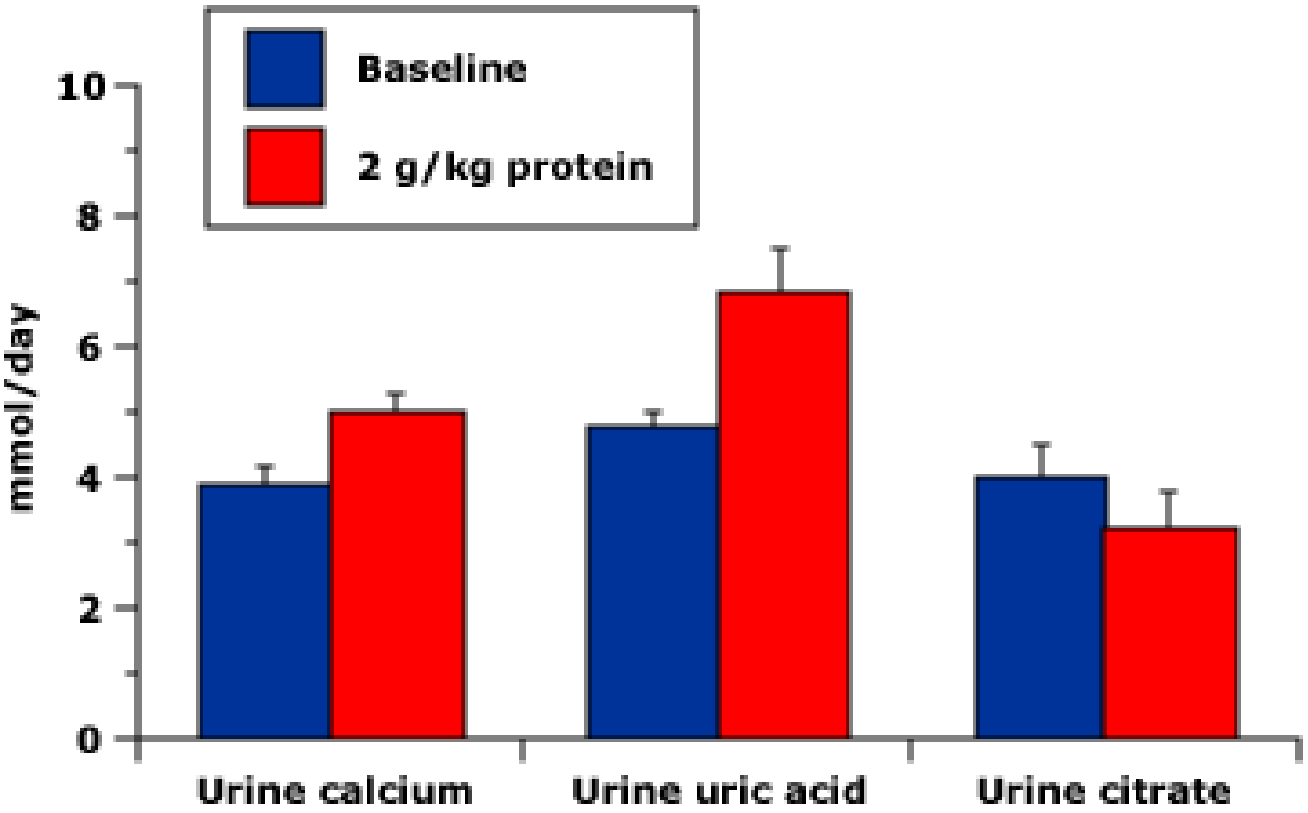
- Originlly felt to be a cause of CaOx stones
- Allopurinol reduced risk of stone formation in pts with high urine uric acid and normal urine calcium (NEJM 1986)
- Recent studies refute this claim: (Curhan KI 2008)

NHS1				NHS2				HPFS			
Uric acid, mg				Uric acid, mg				Uric acid, mg			
<400	353	161	1.00 (Ref.)	<400	159	75	1.00 (Ref.)	<400	116	46	1.00 (Ref.)
400–499	248	116	0.96 (0.69–1.33)	400–499	190	76	1.01 (0.66–1.55)	400–499	79	67	0.48 (0.29–0.80)
500–599	159	59	1.07 (0.70–1.64)	500–599	151	61	0.91 (0.56–1.47)	500–599	115	79	0.49 (0.30–0.80)
600–699	69	40	0.64 (0.37–1.09)	600–699	105	42	0.69 (0.38–1.23)	600–699	112	76	0.41 (0.24–0.68)
700–799	39	16	0.85 (0.40–1.82)	700–799	47	23	0.51 (0.24–1.06)	700–799	82	48	0.38 (0.21–0.68)
800+	30	11	0.72 (0.29–1.80)	800+	51	19	0.44 (0.19–1.02)	800+	132	98	0.22 (0.12–0.40)
P, trend			0.30	*P*, trend			0.06	*P*, trend			<0.001

Management- Diet

- Oral hydration to increase urine volume to over 2L/day
- Low animal protein
- Low salt diet (<150meq/d)
- Normal (or high) calcium diet
  - ***Paradoxic***
- Low oxalate diet
- DASH

Diet- Animal Protein

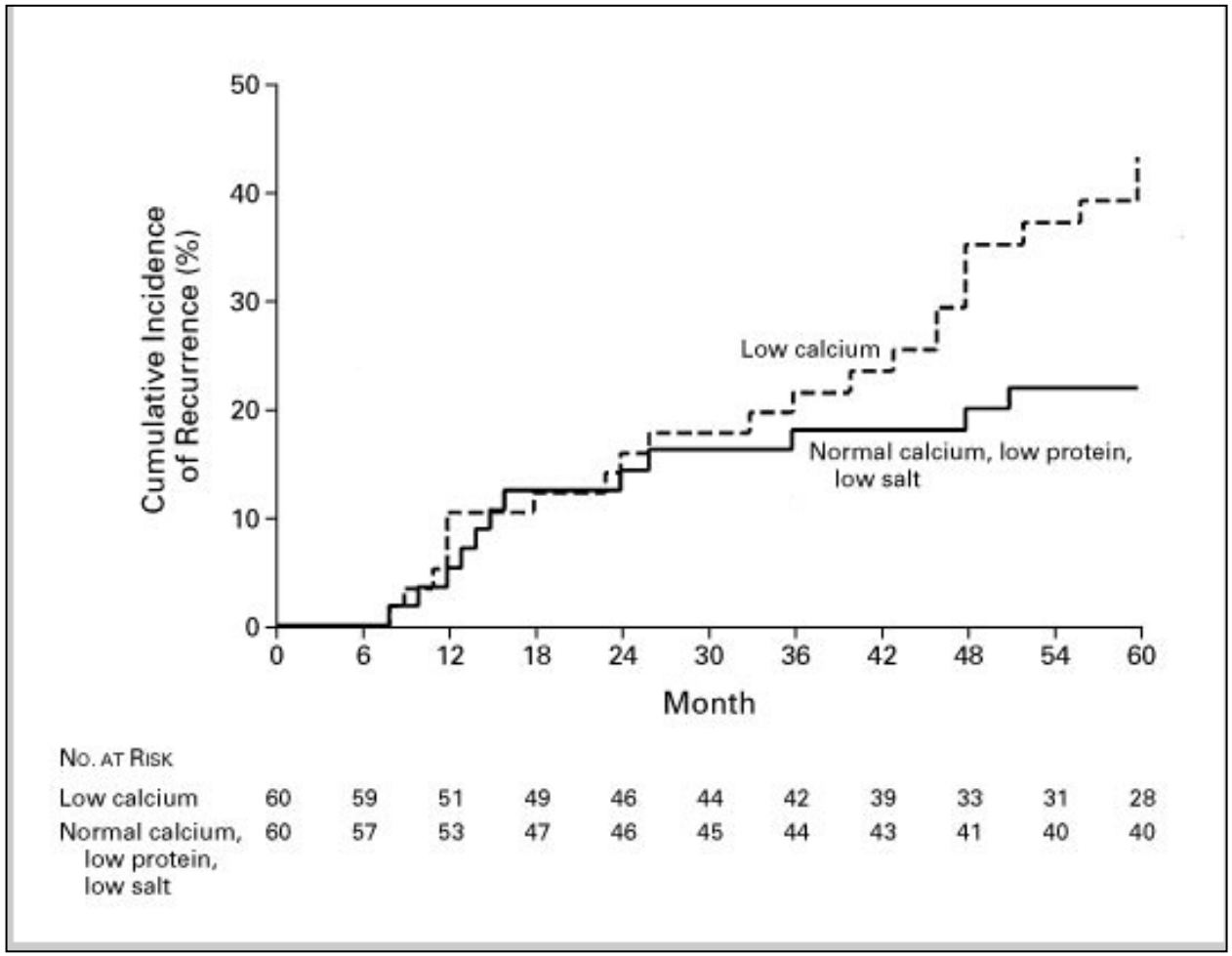


Klok. J Clin Endo Metab. 1989.

Diet- Calcium

- 120 men
- Recurrent CaOx stones
- High urine Ca

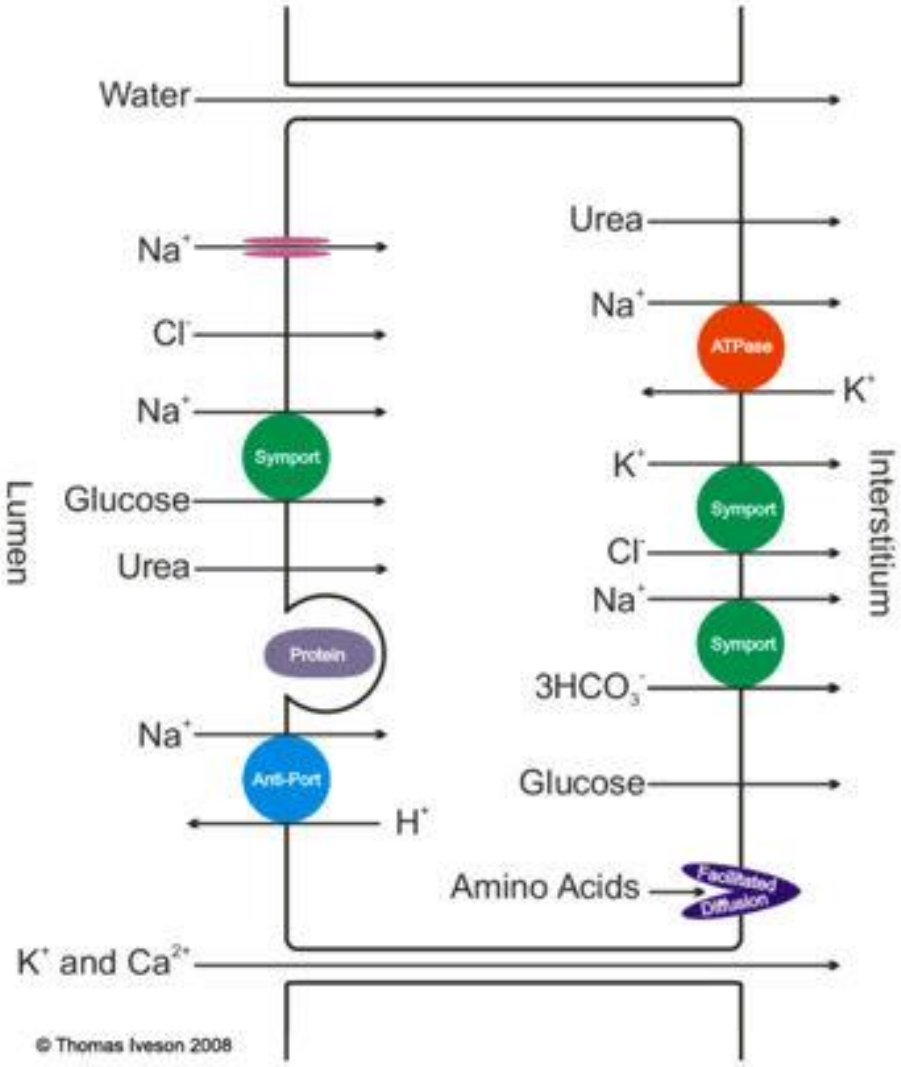
- In tx group, urine oxalate down



Borghi. NEJM. 2002

Diet- Sodium

- Proximal tubule transport
- Inreasing sodium intake from 80- >200meq/d increased urine calcium excretion by 40%



Muldowney, KI 1982.

Diet– Oxalate

- Not much benefit in most populations

Parameter		Quintile					*P* for Trend
		1	2	3	4	5	
HPFS							
	quintile median (mg/d)	106	149	191	236	328	
	cases	363	317	325	313	309	
	person-years	105,806	106,298	107,393	108,200	107,788	
	age-adjusted RR (95% CI)	1.0	0.89 (0.76 to 1.03)	0.89 (0.77 to 1.04)	0.85 (0.73 to 0.99)	0.85 (0.73 to 0.99)	0.04
	multivariate RR (95% CI)[b]	1.0	1.01 (0.86 to 1.17)	1.07 (0.92 to 1.25)	1.10 (0.94 to 1.29)	1.22 (1.03 to 1.45)	0.01
NHS I							
	quintile median (mg/d)	87	127	164	205	287	
	cases	312	279	304	250	269	
	person-years	254,953	257,271	259,528	259,712	258,882	
	age-adjusted RR (95% CI)	1.0	0.89 (0.76 to 1.05)	0.96 (0.82 to 1.12)	0.79 (0.67 to 0.93)	0.85 (0.72 to 1.00)	0.03
	multivariate RR (95% CI)[b]	1.0	1.02 (0.86 to 1.20)	1.16 (0.99 to 1.36)	1.03 (0.87 to 1.23)	1.21 (1.01 to 1.44)	0.05
NHS II							
	quintile median (mg/d)	85	117	157	202	293	
	cases	365	340	296	286	277	
	person-years	169,306	168,806	169,837	169,964	169,674	
	age-adjusted RR (95% CI)	1.0	0.95 (0.82 to 1.10)	0.83 (0.71 to 0.96)	0.80 (0.69 to 0.94)	0.79 (0.67 to 0.92)	0.001
	multivariate RR (95% CI)[b]	1.0	1.03 (0.88 to 1.20)	0.96 (0.82 to 1.13)	1.00 (0.85 to 1.18)	1.06 (0.89 to 1.27)	0.57

Taylor. JASN. 2007

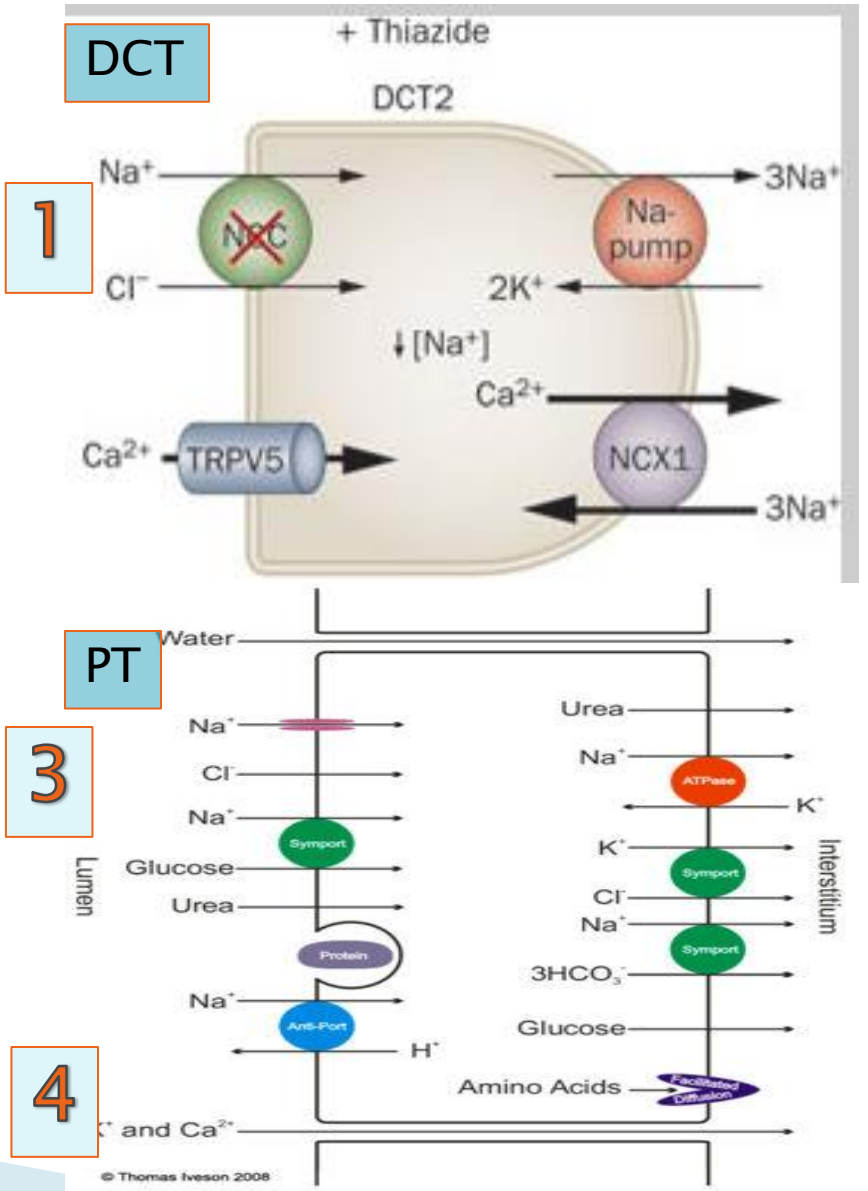
Treatment- Medications

- Indicated if dietary changes not sufficient to prevent worsening stone buden

- Hypercalciuria- Thiazide diuretics
- Hyperuricosuria- Allopurinol(?)
- Hypocitraturia- Alkali Citrate
- Low urine pH- Alkali Citrate

Hypercalciuria – Thiazides

- 1) Inhibition of NCC in DCT
- 2) Volume Depletion
- 3) Increased Na reabsorption in Proximal Tubule
- 4) Increased passive Ca reabsorption



Hypercalciuria – Thiazides

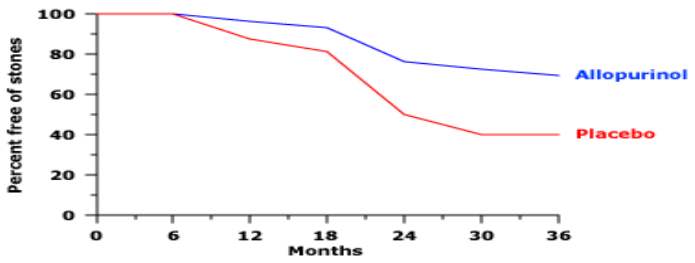
- Chlorthalidone, Indapamide, HCTZ
  - Often require doses greater than used for HTN
- Prevents formation of new stones
  - Does not dissolve preexisting stones

Author, Year	Treatment	Selection/Percent Hypercalciuria	Follow-Up (years)	*n* Treated/*n* Placebo	RR
Brocks, 1981 (17)	Bendroflumethiazide 2.5 mg TID	None	1.6	33/29	NS
Scholz, 1982 (18)	HCTZ 25 mg BID	None	1	25/26	NS
Laerum, 1984 (12)	HCTZ 25 mg BID	None/20%	3	25/25	0.39
Wilson, 1984 (16)	HCTZ 100 mg daily	None	2.8	23/21	0.48
Robertson, 1985 (15)	Bendroflumethazide 2.5 mg TID	None	3 to 5	13/9	0.38
Mortensen, 1986 (13)	Bendroflumethazide 2.5 mg + KCl	None	2	12/10	NS
Ettinger, 1988 (10)	Chlorthalidone 25/50 mg	None/13% to 15.8%	3	19/23/31 25 mg/50 mg/placebo	0.23
Ohkawa, 1992 (14)	Trichlormethiazide 4 mg	Hypercalciuria	2.1 to 2.2	82/93	0.42
Borghi, 1993 (9)	Indapamide 2.5 mg daily	Hypercalciuria	3	43/14	0.21
Fernandez-Rodriguez, 2006 (11)	HCTZ 50 mg daily	None/52%	3	50/50	0.56

Hyperuricosuria – Allopurinol (?)

- Many older trials suggest Allopurinol can reduce calcium stone formation
- Curhan 2008- protective effect of hyperuricosuria?
- No trials in uric acid stones
  - Rec: Tx if Hyperuricosuria AND still forming stones despite correcting urine pH and volume

Allopurinol prevents stones in hyperuricosuria



When compared to placebo, allopurinol protects against new stone formation in hyperuricosuric calcium oxalate stone formers.

Data from Ettinger, B, Tang, A, Citron, JT, et al, N Engl J Med 1986; 315:1386.

Hypocitraturia- Alkali

- Potassium Citrate 20-60meq/d in divided doses
- Sodium Citrate/Bicarbonate

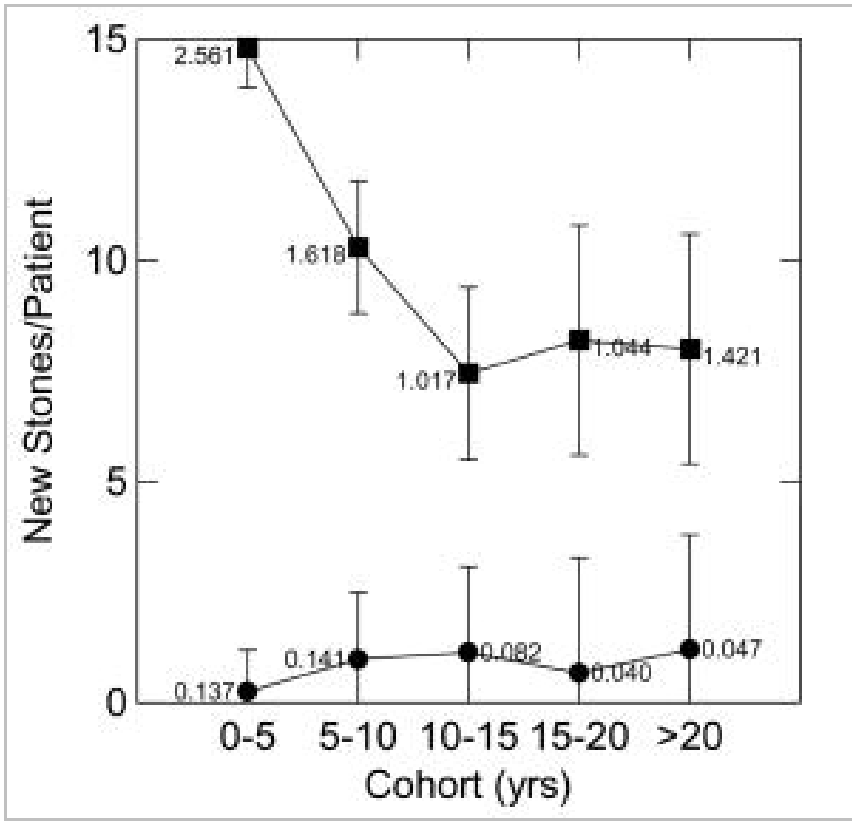
- Barcelo, J Uro, 1993. Significant remission: Kcitrate (72%) vs Placebo (20%)

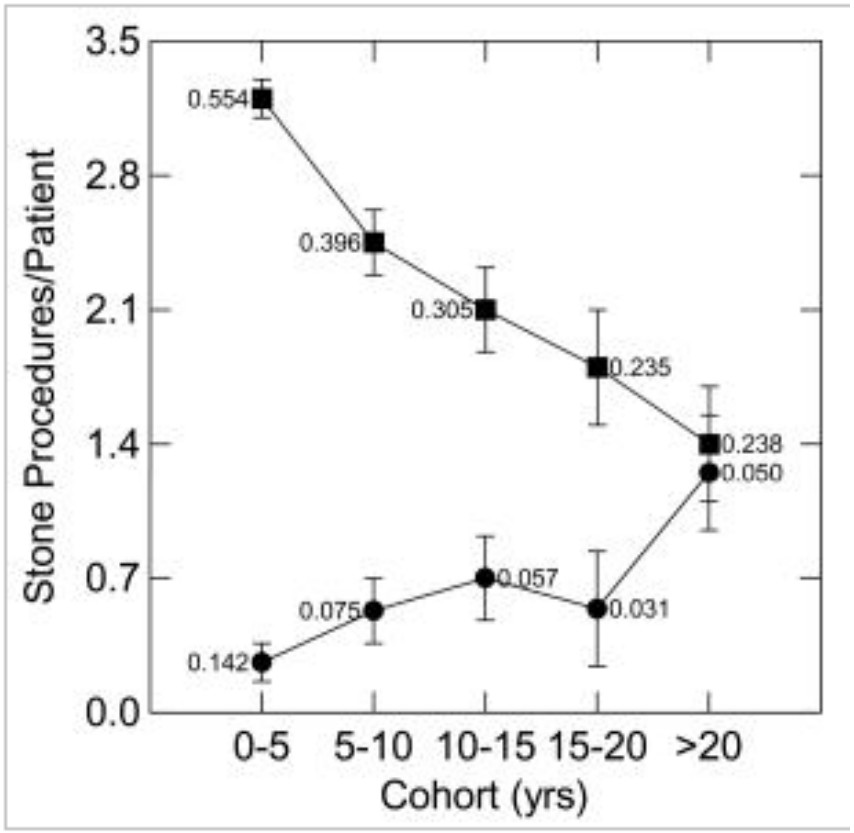
- Fink, Annals, 2013. Recurrent stone risk, RR = 0.25 with citrate tx

- Setzer, J Uro, 1996. Lemonade significantly increased urine citrate levels ~200mg/day

Is medical therapy worth it?

- UChicago stone clinic follow-up over time





Parks, Coe, BJU 2009

Treatment Summary

- Calcium Oxalate:
  - Diet: High fluid, Low salt, Low animal protein, low oxalate
  - Meds: Citrate, Thiazide, Allopurinol?
- Calcium Phosphate
  - Diet: High fluid, Low salt, Low animal protein
  - Meds: Citrate (watch pH!), Thiazide, Allopurinol?
- Uric Acid
  - Diet: High fluid, Low salt, Low animal protein
  - Meds: Citrate, Allopurinol?
- Struvite
  - Not much
- Cystine
  - Diet: High fluid, Low animal protein
  - Meds: Citrate, Thiols (increase water solubility)

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Thank you!