



**Brigham and Women's Hospital**

Founding Member, Mass General Brigham

# Metabolic Management of Kidney Stones

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Clinical focus: Nephrolithiasis

Research focus: Nephrolithiasis, CKD, Gout, Hearing Loss, Tinnitus, Shingles



# DISCLOSURES

I have financial relationships or affiliations with:

<u>Name of Organization</u>	<u>Relationship</u>
UpToDate	Section Editor, Author
GSK	Grant Support
OM1	Equity
Atom Bioscience	Consultant



# **Kidney Stones Can Be Prevented**

# OBJECTIVES

Use case vignettes to:

Review the presentation and evaluation of patients with different types of kidney stones

Review the approaches to prevent stone recurrence



## Case #1—Mr. M.T.

- 52 y.o. male with recurrent nephrolithiasis
- Passing small pieces, orange colored, “continuously
- PMH: ulcerative colitis, s/p colectomy
- Meds: finasteride, SSRI, vitamin D, acyclovir

# Case #1—Evaluation

- Blood
  - Bicarbonate 28 meq/L
  - Creatinine 1.40 mg/dl
  - Calcium: 9.3 mg/dl
  - Uric acid: not measured
- No recent imaging

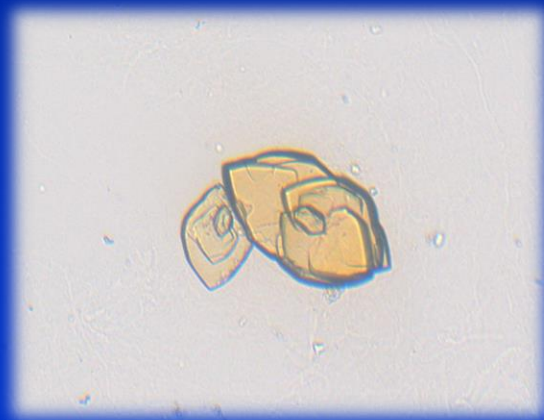
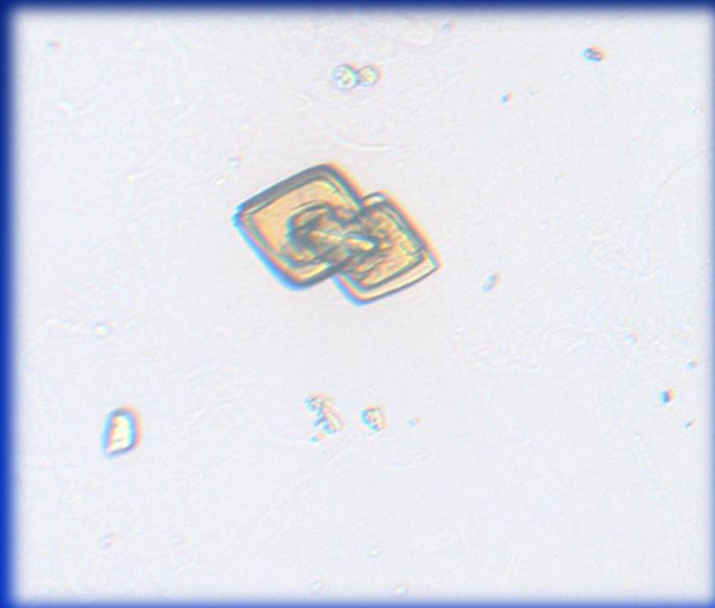
# Renal Consult Requested

- Stone type?
- Evaluation?
- Treatment?



# What Is the Most Likely Stone Type?

- A. Calcium oxalate
- B. Calcium phosphate
- C. Uric acid
- D. Cystine

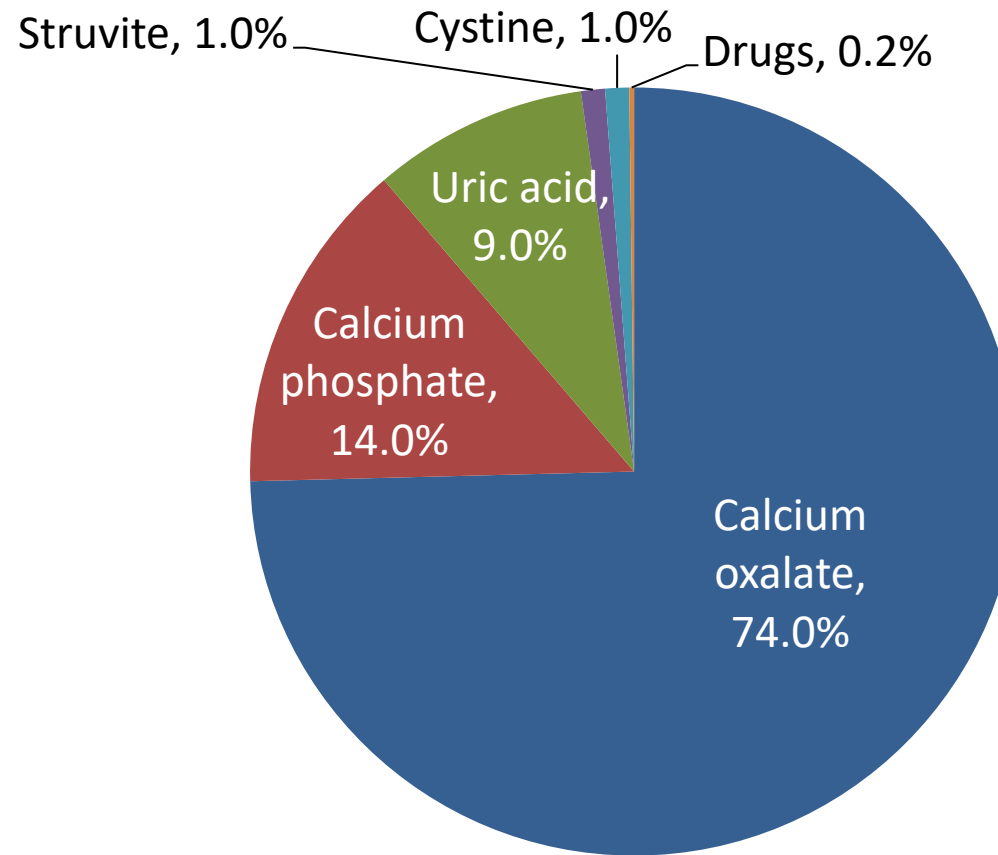


# Answer: Uric Acid

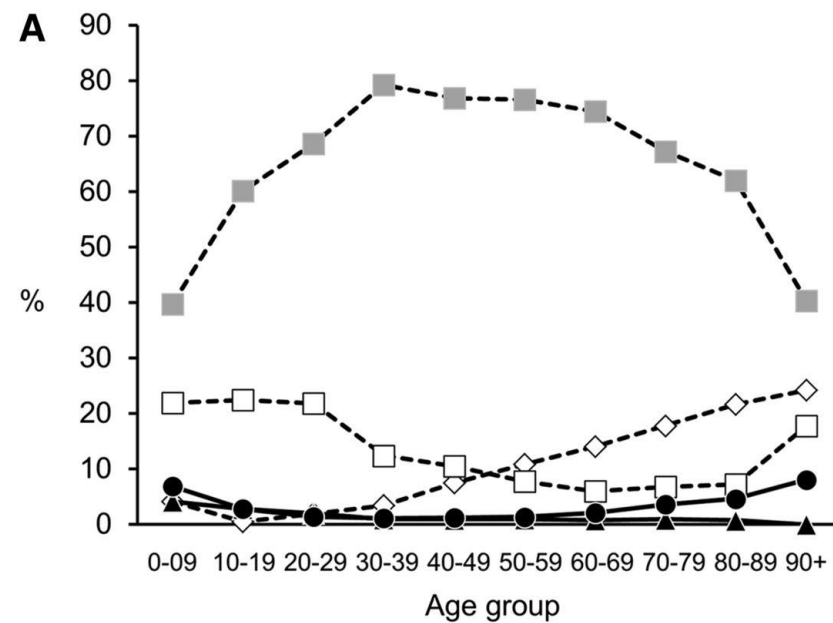
- Rapid stone formation
- Chronic GI losses → persistently acidic urine



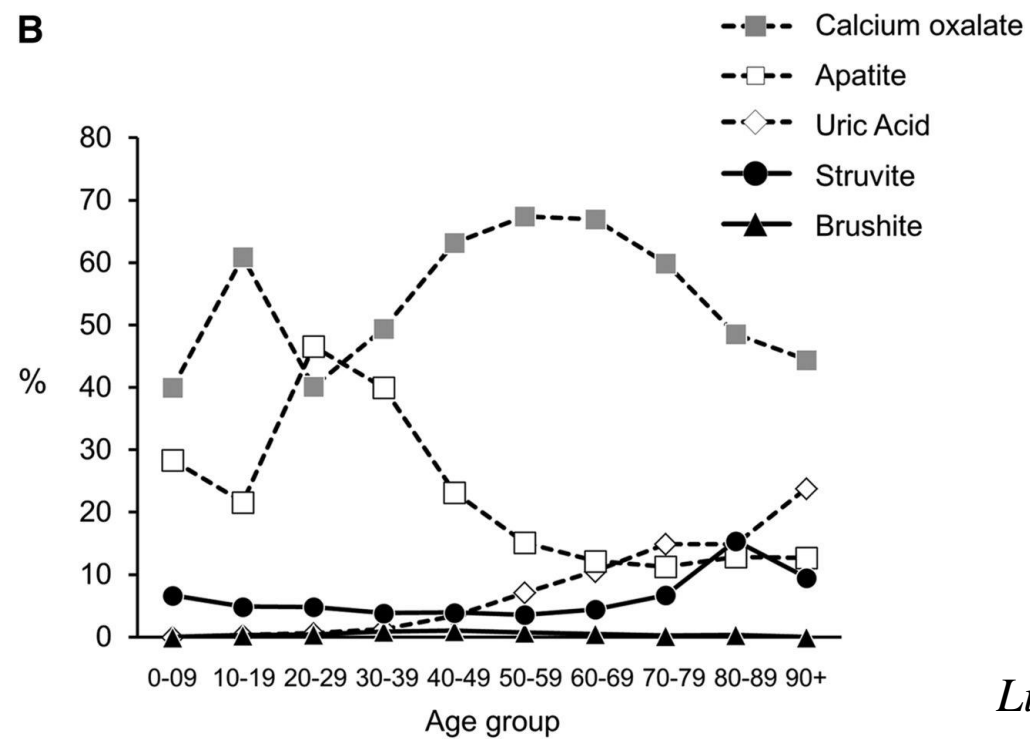
# Types of Stones in First Time Stone Formers



Men



Women



# Types of Stones and Causes

- **Calcium oxalate**—low urine volume, high calcium, high oxalate, low citrate
- **Calcium phosphate**—low urine volume, alkaline urine, high calcium, low citrate, high phosphate
- **Uric acid**—persistently acid urine, high urine uric acid
- **Cystine**—autosomal recessive disorder
- **Struvite**—urease producing bacteria in upper tract

## Case #1—Mr. G.O.

- 52 y.o. male with recurrent nephrolithiasis
- Passes a stone every two months
- PMH: chronic diarrhea
- Meds: antidiarrheal; allopurinol 300 mg/d



## Case #1—24 hour urine

<u>TV</u>	<u>Ca</u>	<u>Ox</u>	<u>Cit</u>	<u>UA</u>	<u>Creat</u>	<u>Na</u>	<u>pH</u>
2.4	290	56	141	503	2599	347	5.6
1.5	172	20	142	231	1528	237	5.3

# Question: Metabolic abnormalities?

Which urine is the correct one?

<u>TV</u>	<u>Ca</u>	<u>Ox</u>	<u>Cit</u>	<u>UA</u>	<u>Creat</u>	<u>Na</u>	<u>pH</u>
2.4	290	56	141	503	2599	347	5.6
1.5	172	20	142	231	1528	237	5.3

# Question: Metabolic abnormalities?

*Assume first urine is the correct one.*

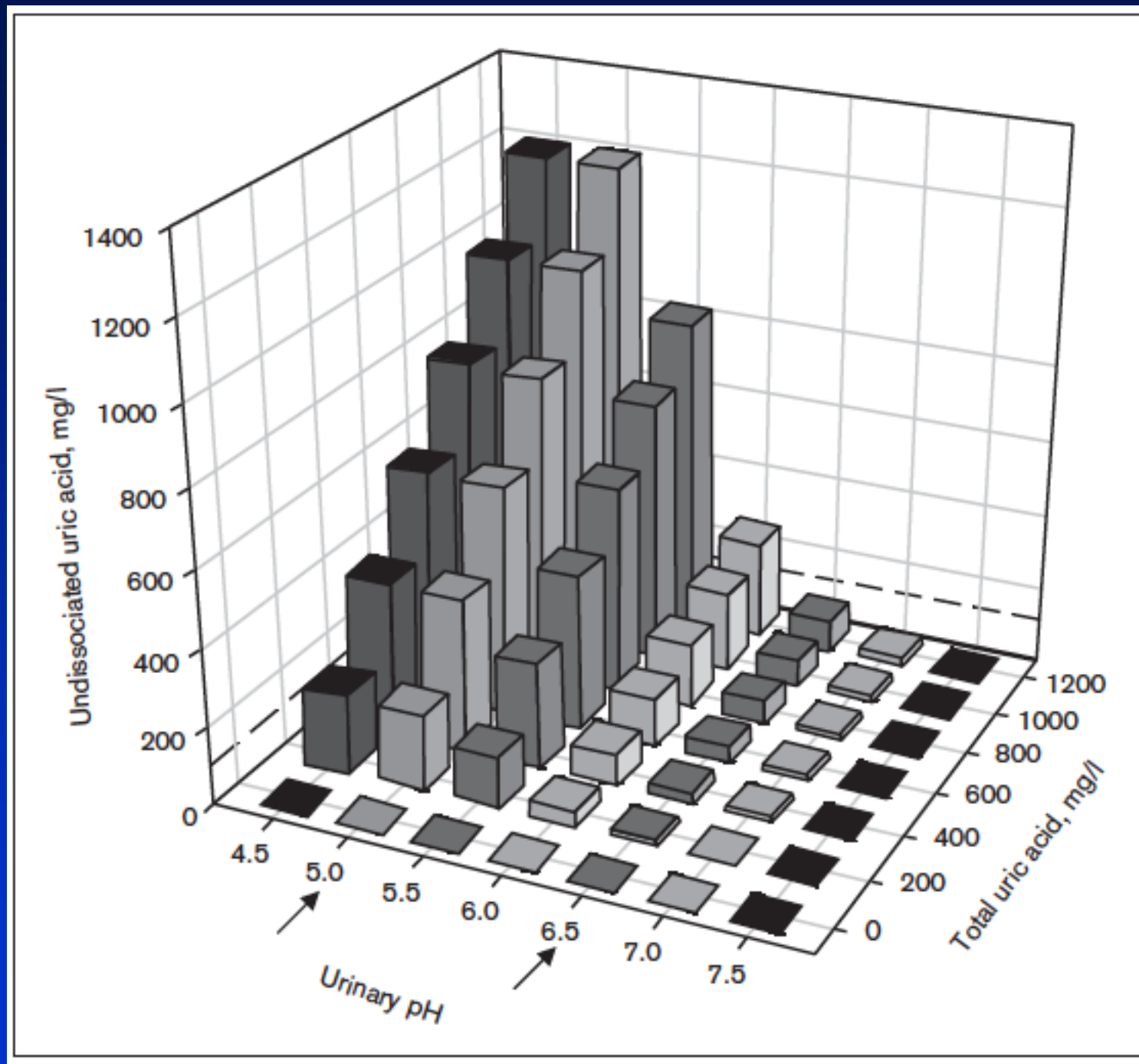
- High calcium, oxalate, sodium
- Low citrate
- Normal uric acid

*Assume second urine is the correct one.*

- High, sodium
- Low citrate
- Normal calcium, oxalate, uric acid

# Question: Next Steps?

- Imaging study  
Spiral CT
- Repeat 24-hour urine
- Alkalinization of urine—urine pH is most important risk factor for uric acid stones
  - Potassium citrate or bicarbonate (40-80 meq/d)
  - Patient checks urine pH (aim for ~6.5 or higher)



## Case #2—Ms. G.K.

- 45 y.o. female with recurrent nephrolithiasis
- Frequency: every 8-10 months
- Previous procedures:
  - ESWL x 5
  - Cystoscopy x 6
  - PCNL x 1
- PMH—otherwise negative

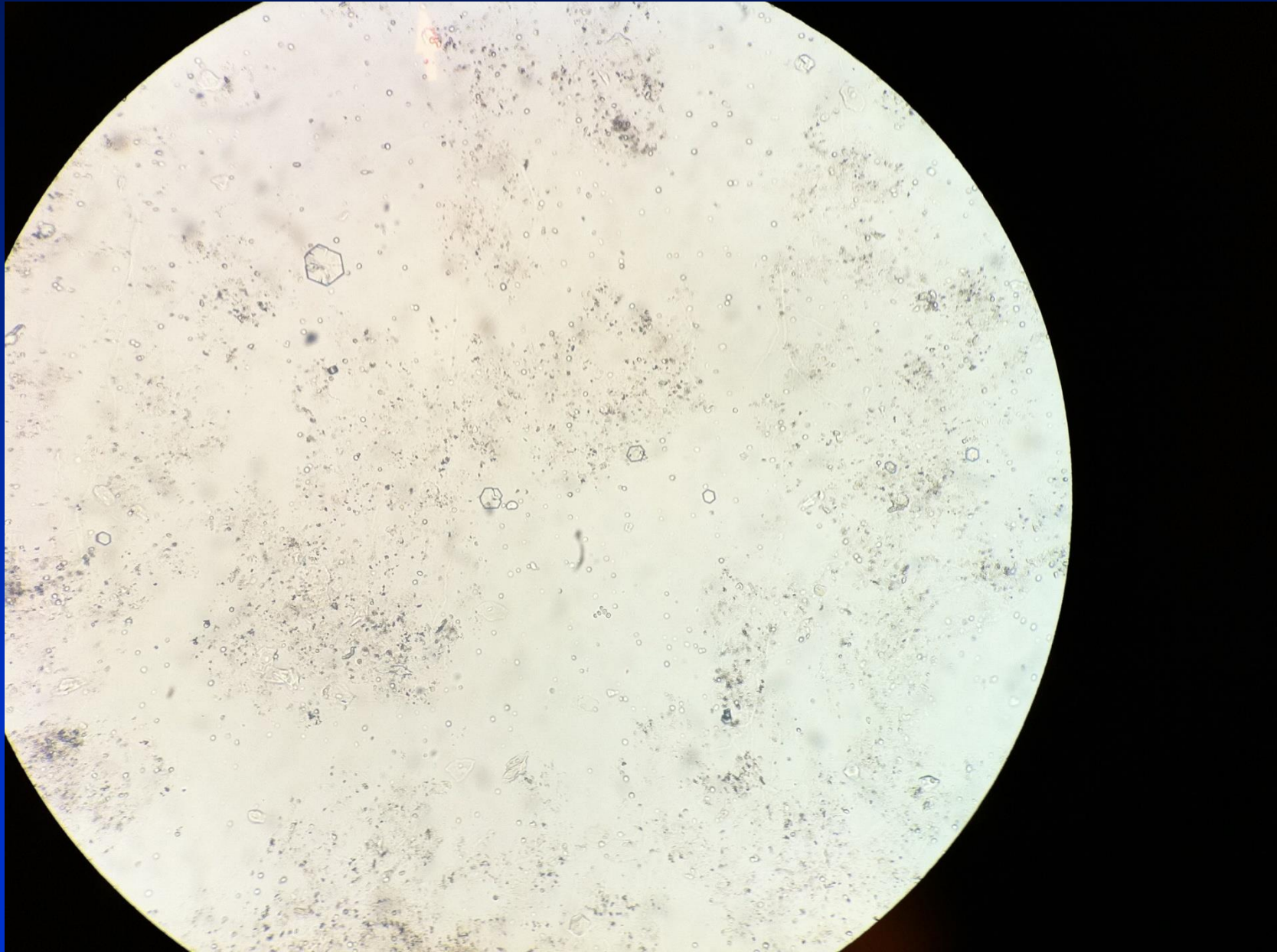
## Case #2—24-hour urine

<u>TV</u>	<u>Ca</u>	<u>Ox</u>	<u>Cit</u>	<u>UA</u>	<u>Creat</u>	<u>Na</u>	<u>pH</u>
2.30	114	28	1102	396	972	168	7.30

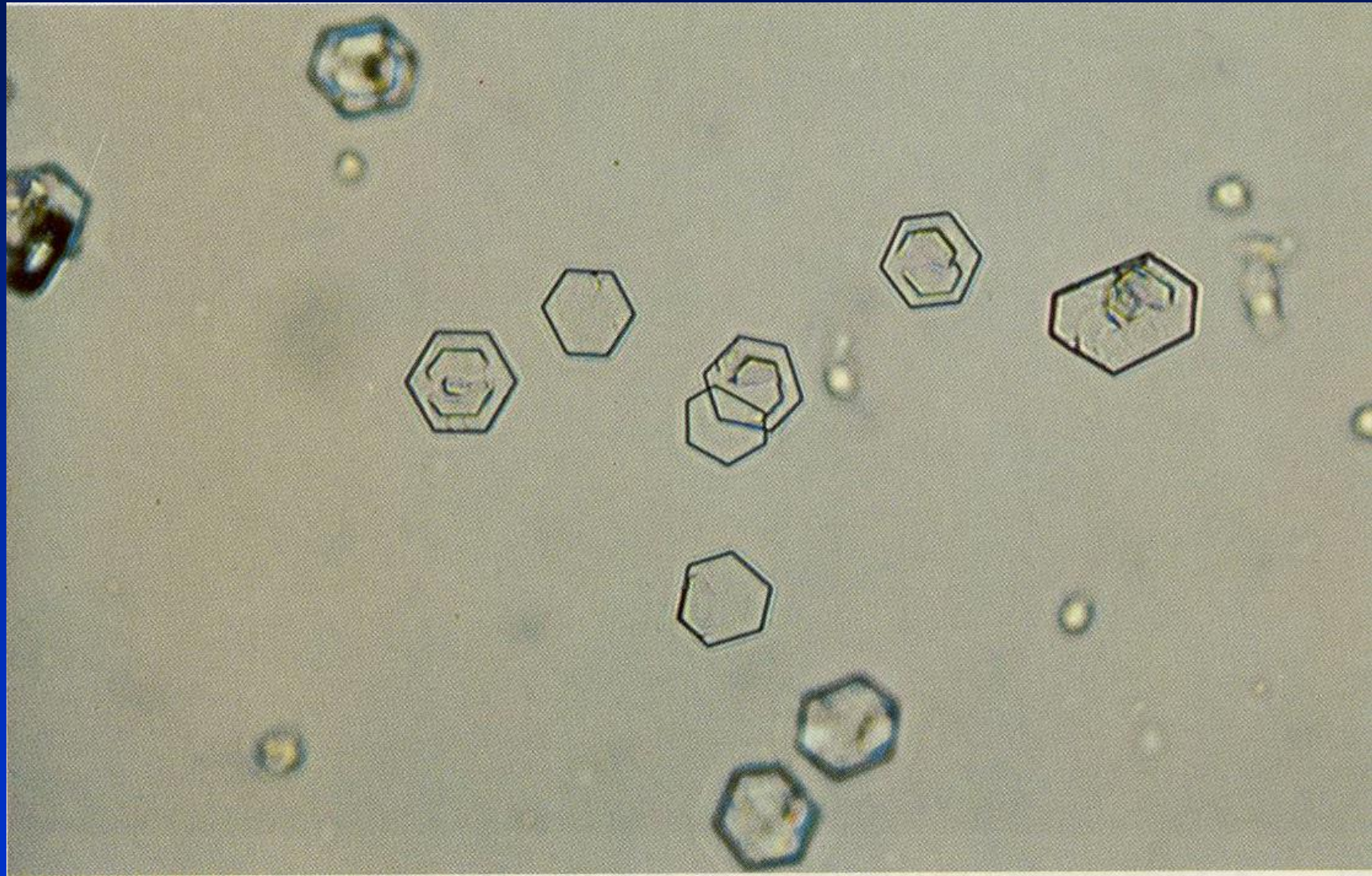
# What Is the Most Likely Stone Type?

- A. Calcium oxalate
- B. Calcium phosphate
- C. Uric acid
- D. Cystine









# Answer: Cystine

- Autosomal recessive disorder
- Excessive excretion of cystine, which is poorly soluble

# Medications

- Potassium citrate 20 meq BID
  - Occasionally checks urine pH
- Allergies
  - Penicillamine → rash

# CT Report

Right kidney is normal

Left kidney: 4 mm and 2 mm upper pole stones; 9 mm lower pole stone

4 mm stone at left ureterovesical junction

## Case #2—24-hour urine

<u>TV</u>	<u>Ca</u>	<u>Ox</u>	<u>Cit</u>	<u>UA</u>	<u>Creat</u>	<u>Na</u>	<u>pH</u>
2.30	114	28	1102	396	972	168	7.30

Total cystine: 1877 mg/d (816 mg/L)

# Treatment

- Reduce [cystine] < 250mg/L
- Increase fluid intake?
  - Urine output required > 7 L/d
- Tiopronin (Brand name: Thiola)
  - Typically need at least 900 mg/d (300 mg TID)
  - Extended release formulations available
- Continue alkalinization aiming for pH >7.0

## Case #2—6 Months Later...

- Calls with left renal colic
- Stopped medication because it clearly did not work
- Is she correct?





Shift Overlay from 60xx to 7FE0

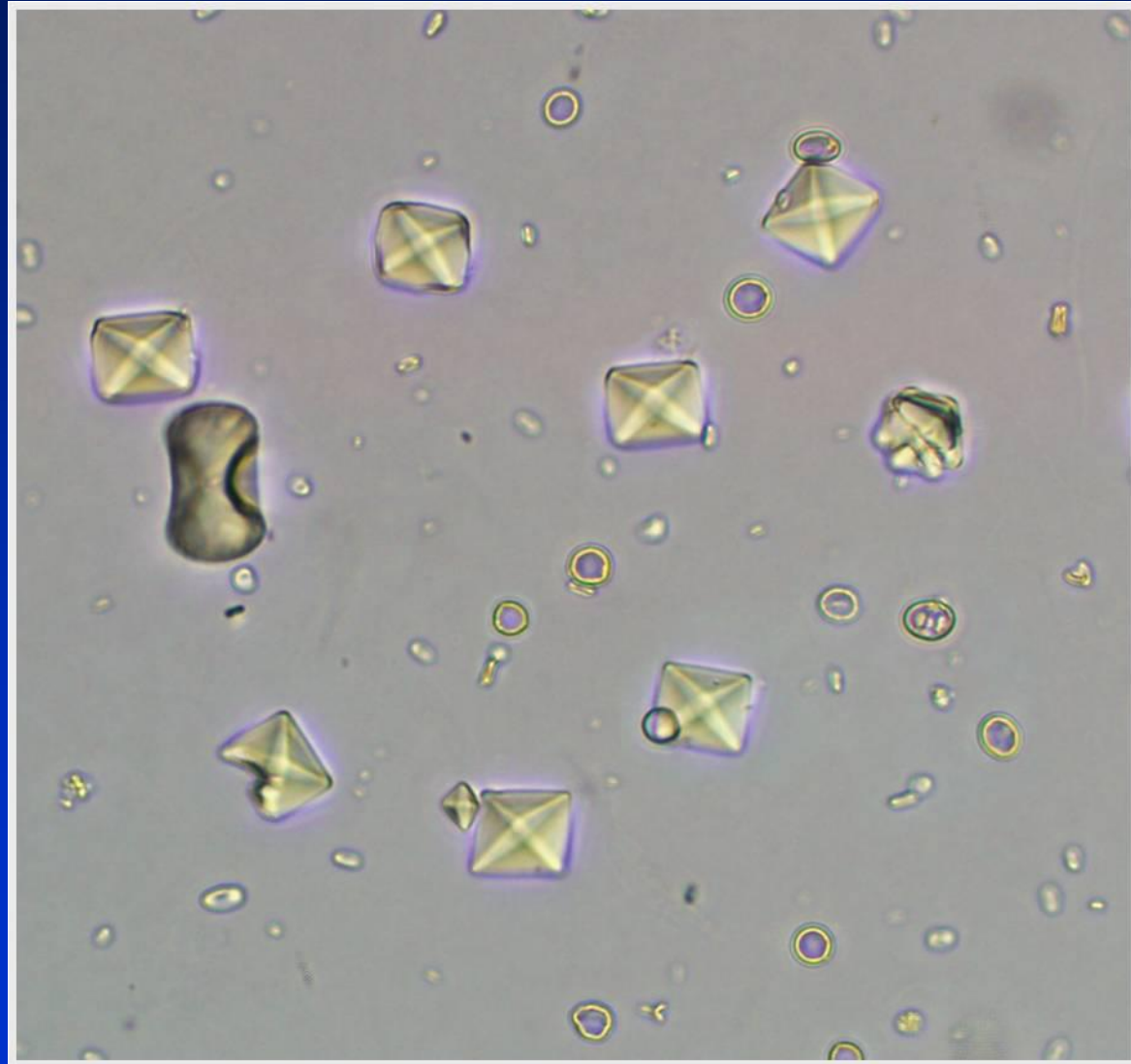


## Case #3—Ms. J.B.

- 35 y.o. female nurse with recurrent stones
- Presented 5 years before with colic and bilateral renal stones
- PMH: unremarkable

# What Is the Most Likely Stone Type?

- A. Calcium oxalate
- B. Calcium phosphate
- C. Uric acid
- D. Cystine



*Courtesy of John Lieske*

Answer:	Calcium oxalate	95%
	Calcium phosphate	5%

- Mixed calcium stones common
- Calcium oxalate most common crystal type
- Randall's plaque composed of calcium phosphate
  - Calcium oxalate grows on top of Randall's plaque

# CT Report

## Bilateral renal stones

- Need to ask radiologists to quantify number and size
- Also need description if stone burden has changed over time

3 mm stone at left UVJ

# Question: Acute Management?

- Watchful waiting
  - For how long?
    - Pain
    - Infection
    - Hydronephrosis
- Medications
  - Alpha blocker
- Cystoscopic removal
- ESWL

## Case #3—24-hour urine

<u>TV</u>	<u>Ca</u>	<u>Ox</u>	<u>Cit</u>	<u>UA</u>	<u>Creat</u>
1.73	210	26	845	493	1400
1.10	209	32	943	447	1265



# Urinary Risk Factors for CaOx Stones

## Increased risk

Calcium

Oxalate

## Decreased risk

Citrate

Volume

*But need to rethink our approach--these  
are continuous variables, not dichotomous*

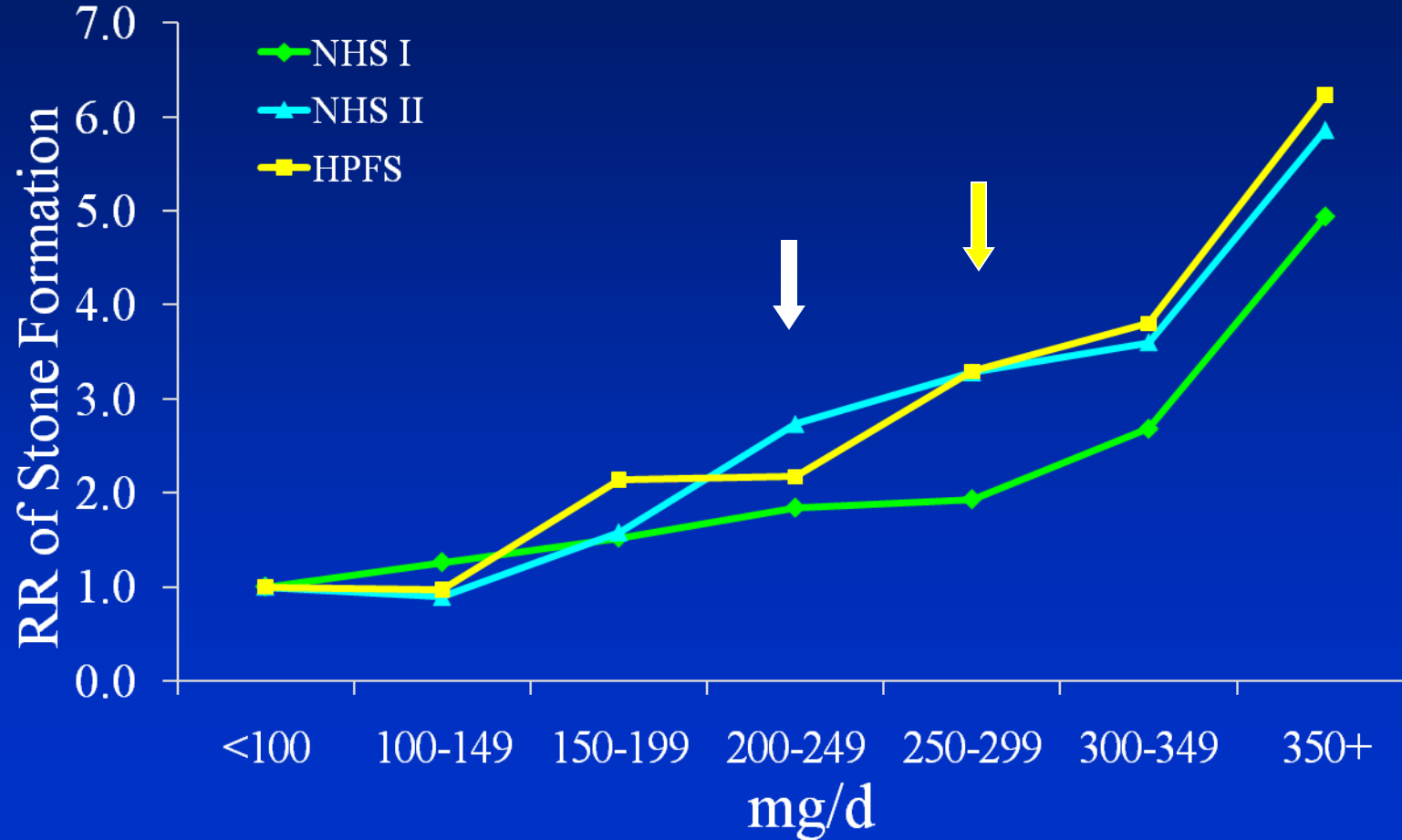
# “Definitions”

- Hypercalciuria
  - Males:  $> 300$  mg/d
  - Females:  $> 250$  mg/d
  - Either:  $> 4$  mg/kg/d
- Hyperoxaluria:  $> 45$  mg/d
- Hyperuricosuria
  - Males:  $> 800$  mg/d
  - Females:  $> 750$  mg/d

# Question: Treatment?

- Increase fluid intake
  - How much to prescribe?
- If TV does not increase?
- Thiazide

# 24 Hour Urine Calcium



**Table S12: Secondary End Point Analysis: Radiologic Stone Recurrence.**

<b>Group</b>	<b>Patients</b>	<b>Events</b>	<b>% (No. Events/ No. Patients)</b>	<b>Odds Ratio (95% CI)</b>
Placebo	94	46	49%	Reference
12.5 mg HCT	98	44	45%	0.85 (0.48-1.50)
25 mg HCT	101	32	32%	0.49 (0.27-0.87)
50 mg HCT	90	31	34%	0.54 (0.29-0.98)

# Question: Follow-Up?

- Repeat 24-hour urine
  - 4-6 weeks
- Adjust recommendations
- Repeat 24-hour urine
- Follow-up imaging
  - Stone growth
  - New stone formation

# Advice Based on Experience

- Always measure TWO 24-hour urines at baseline
- Find out stone composition by analysis
- Repeat 24-hour urine after recommendations
- Challenging for patients to reduce sodium intake
- Helical CT is the most reliable imaging study

# Advice Based on Experience

- Be careful when recommending an overly restrictive low oxalate diet
- Explain to patient that a new episode of colic does not always mean treatment failure
- The urologist is your friend



1. A 42 year old male suffered a severed spinal cord at T10. He has a long history of recurrent urinary tract infections. As part of the evaluation for abdominal pain, he had a KUB that showed a staghorn calculus in his right kidney. One of his urine infections most likely included which of the following bacteria?
  - a. E. coli
  - b. MRSA
  - c. Klebsiella pneumoniae
  - d. proteus mirabilis

(Correct answer is D)

# Answer: Struvite

- Proteus is the most common urease producing bacteria
- Struvite stones only form when there is a urease producing bacterium in the upper tract.

2. A child whose parents are first cousins was found to have a kidney stone at age 7. The urinalysis showed blood and many hexagonal crystals. The most likely stone composition is:
- a. cystine
  - b. struvite
  - c. calcium oxalate
  - d. uric acid

(correct answer is A)

# Answer: Cystinuria

- Cystinuria is an autosomal recessive disorder
- Excessive cystine excretion results in crystal formation
- Cystine crystals have a characteristic hexagonal shape

# Additional Case

## Case #4—Mr. S.L.

- 49 y.o. male accountant with h/o Crohn's disease
- S/p partial ileal resection
- Recurrent intestinal obstruction
- Presented 6 months ago with abdominal pain
- Intestinal obstruction?
- Exploratory laparotomy planned

## Case #4—Mr. S.L.

- Pre-op evaluation: U/A-->100 RBC
- Underwent right hemi-colectomy
- POD #5—abdominal pain
  - due to tapering of analgesics?
- Discharged home on oxycodone
- Returned two days later to ER
- UVJ stone seen on CT

# Question: Stone type?

- A. Calcium oxalate
- B. Calcium phosphate
- C. Uric acid
- D. Cystine

Calcium oxalate 100%



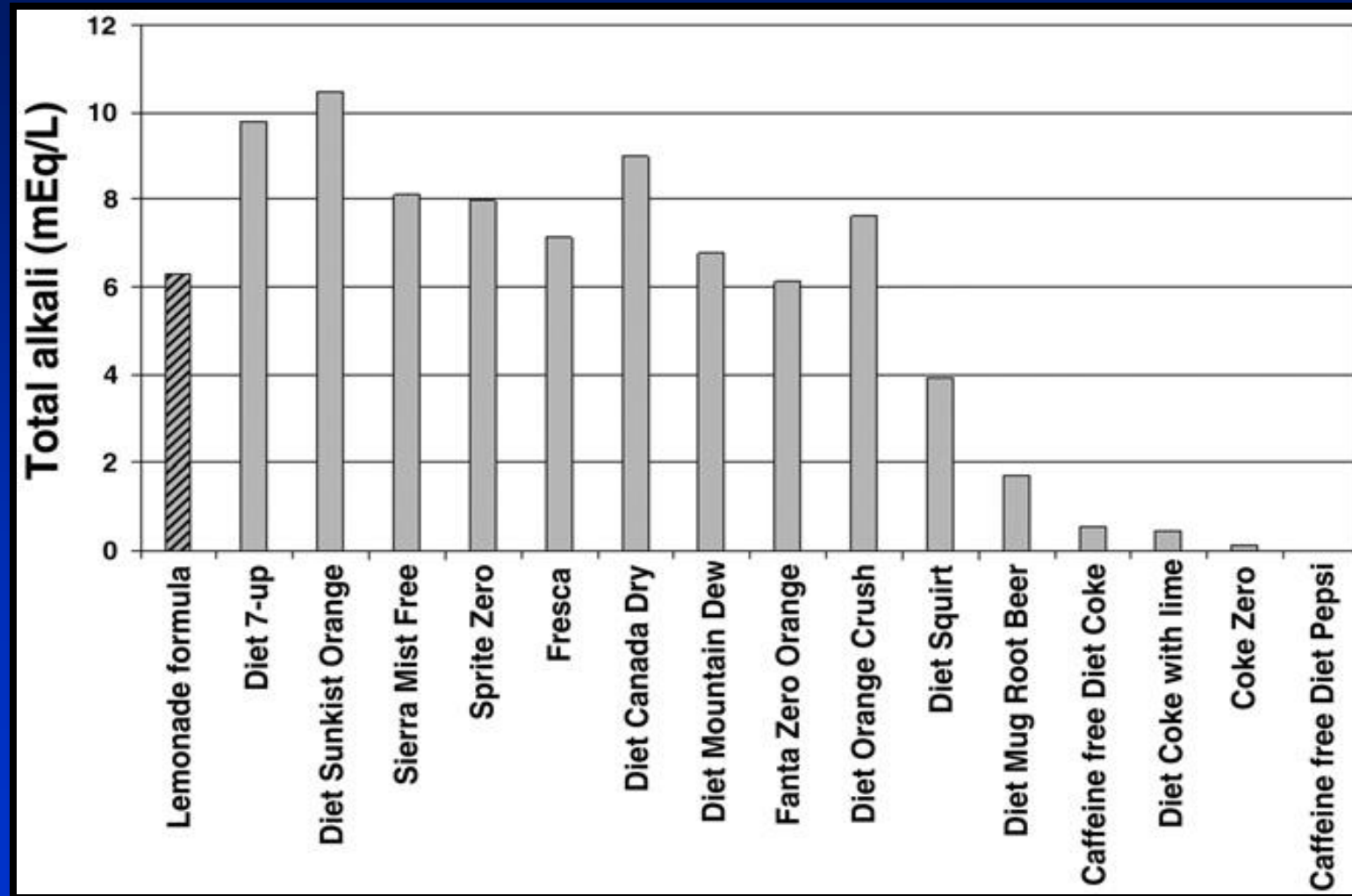
## Case #4—24 hour urine

<u>TV</u>	<u>Ca</u>	<u>Ox</u>	<u>Cit</u>	<u>UA</u>	<u>Creat</u>	<u>Na</u>
1.20	62	117	18	413	1350	---
1.30	73	73	11	711	1412	---

# Question: Treatment?

- Increase fluid intake
  - How much to prescribe?
- Reduce oxalate
  - Increase dietary calcium intake
- Increase citrate
  - Which formulation?

# Soda, Lemonade and Citrate



# TAKE HOME MESSAGES

- Kidney stones can be prevented
- Recommendations should be guided by 24-hr urine chemistries. These are continuous values and there is no absolute cutoff for “normal”.
- Obtain 24-hour urine collections to guide initial recommendations and perform follow-up collections to monitor the effectiveness of recommendations.
- Dietary and pharmacologic interventions can substantially reduce risk of stone growth and new stone formation
- Long-term follow-up will help ensure patients continue to follow recommendations.



# REFERENCES

- Pearle MS, Goldfarb DS, Assimos DG, Curhan GC, Denu-Ciocca CJ, Matlaga BR, Monga M, Penniston KL, Preminger GM, Turk TM, White JR. Medical Management of Kidney Stones: AUA Guideline. *J Urol*. 2014 Aug;192(2):316-24 (AUA guidelines)
- Prochaska ML, Taylor EN, Curhan, GC. Insights Into Nephrolithiasis From the Nurses' Health Studies. *Am J Public Health*. 2016 Sep;106(9):1638-43
- Prochaska M, Taylor E, Ferraro PM, Curhan G. Relative Supersaturation of 24-Hour Urine and Likelihood of Kidney Stones. *J Urol*. 2018 May;199(5):1262-1266.
- Rodriguez A, Curhan GC, Gambaro G, Taylor EN, Ferraro PM. Mediterranean diet adherence and risk of incident kidney stones. *Am J Clin Nutr*. 2020 May 1;111(5):1100-1106
- Dhayat NA, Bonny O, Roth B, et al. Hydrochlorothiazide and Prevention of Kidney-Stone Recurrence. *N Engl J Med* 2023;388:781-91.
- Li D-F, Gao Y-L, Liu H-C, et al. Use of thiazide diuretics for the prevention of recurrent kidney calculi: a systematic review and meta-analysis. *J Transl Med* (2020) 18:106
- Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med*. 1993 Mar; 328(12):833-8.



# CLINICAL TRIALS

Clinical Trials	Change in Management	
Hydrochlorothiazide and Prevention of Kidney-Stone Recurrence (NEJM 2023;388:781-91)	No change in management	Thiazide group had lower risk of new stone formation but not for primary outcome
WHI—calcium supplements (N Engl J Med 2006; 354:669-683)	Use caution when prescribing calcium supplements in patients with a history of kidney stones	Check 24-hr urine calcium before and after starting.
Ultrasonography versus computed tomography for suspected nephrolithiasis(N Engl J Med. 2014 Sep 18;371(12):1100-10); Editorial (N Engl J Med 2014; 371:1154-1155)	Ultrasound can be considered but many patients will likely need a CT (ideally, low-dose CT to limit radiation exposure)	

