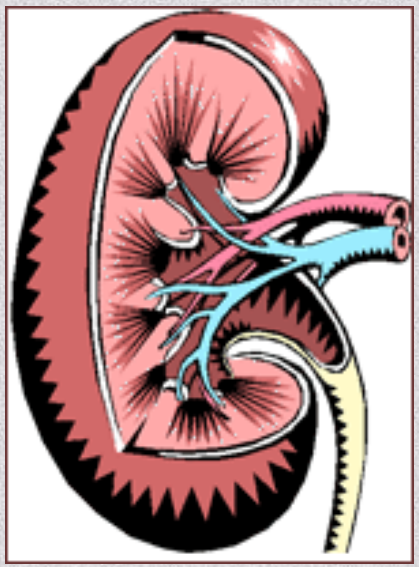
Medical Approach to Nephrolithiasis



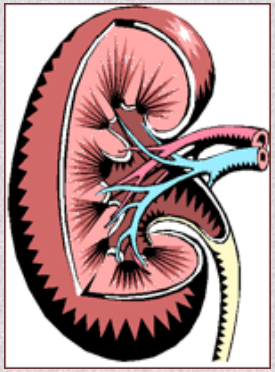
Seth Goldberg, MD

September 15, 2017

ACP Meeting

Washington University in St. Louis
SCHOOL OF MEDICINE

DISCLOSURES



Seth Goldberg, MD
Assistant Professor of Medicine

Research support

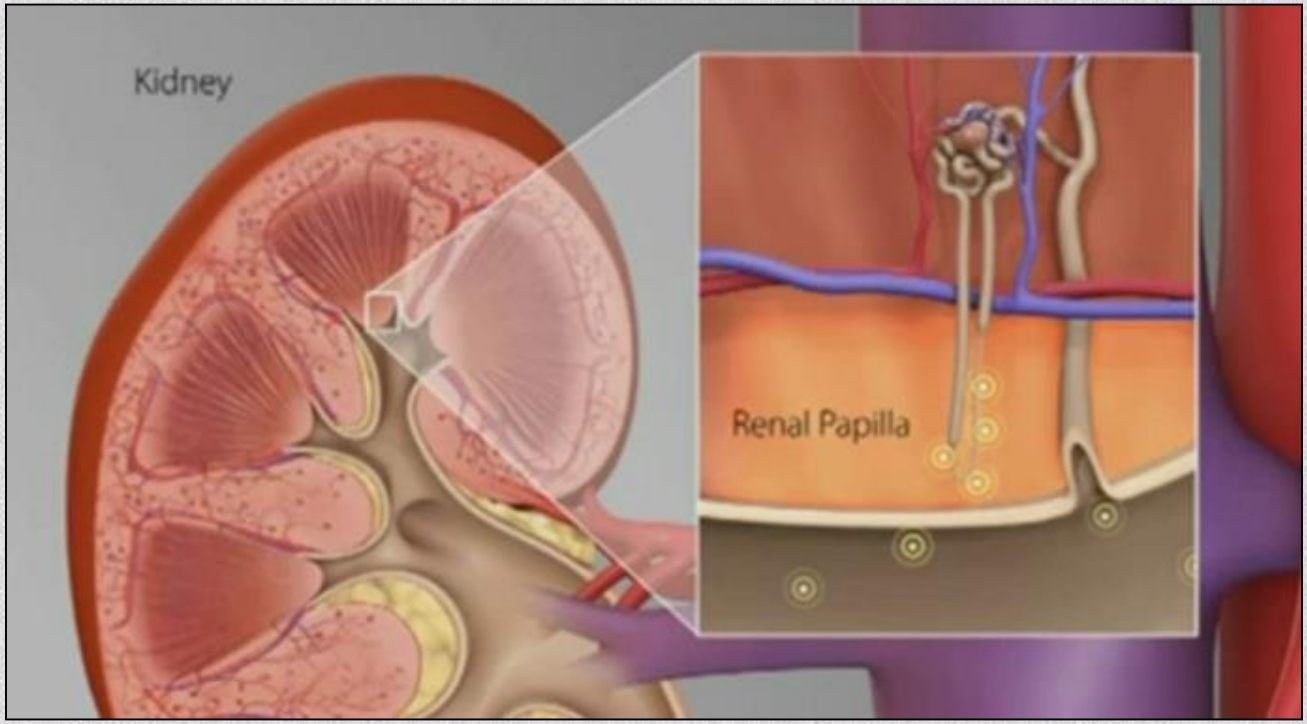
- Abbott
- Kadmon
- Otsuka
- Pfizer

Introduction

- Nephrolithiasis is a common disorder estimated to account for 1% of all hospital admissions
- Men are affected at a rate 3-4x that of women
- 1 in 12 men will experience a kidney stone at some point in his life

Introduction

- Despite the long history of nephrolithiasis, a unifying theory for stone formation has yet to emerge



Vezzoli G, et al, KI, 2010

Introduction

- The initial presentation most frequently involves the severe and sudden onset of unilateral flank pain, radiating to the groin and the finding of microscopic hematuria is common (90%)
- Plain x-rays may reveal most stone types if they are larger than 2mm in diameter (except for uric acid)
- Non-contrast CT is the preferred imaging modality

Introduction

- For the first episode. . . appropriate urologic treatment & general dietary recommendations
- But, resist the temptation to check an extensive stone-risk panel while the patient is in the hospital
- The risk of a second stone is ~50% in the next seven years

Introduction

- A second episode does merit a more complete evaluation, once the patient is back on his or her typical outpatient diet
- 1) Dietary assessment
- 2) Stone analysis (if available)
- 3) 24-hour urine stone battery

General Approach

- Regardless of the stone composition, there are a few common approaches:

- 1) INCREASE FLUIDS
  - Goal >2 L/d UOP
- 2) RESTRICT SODIUM
  - <2-3 gm/d
- 3) “NORMAL” CALCIUM INTAKE
  - Avoid calcium supplements
- 4) LOW PURINE DIET
  - Animal proteins

Stone Types

Calcium Oxalate

Uric acid

Calcium phosphate

Cystine

Struvite ($Mg\text{-}NH_4\text{-}PO_4$)

Stone Types

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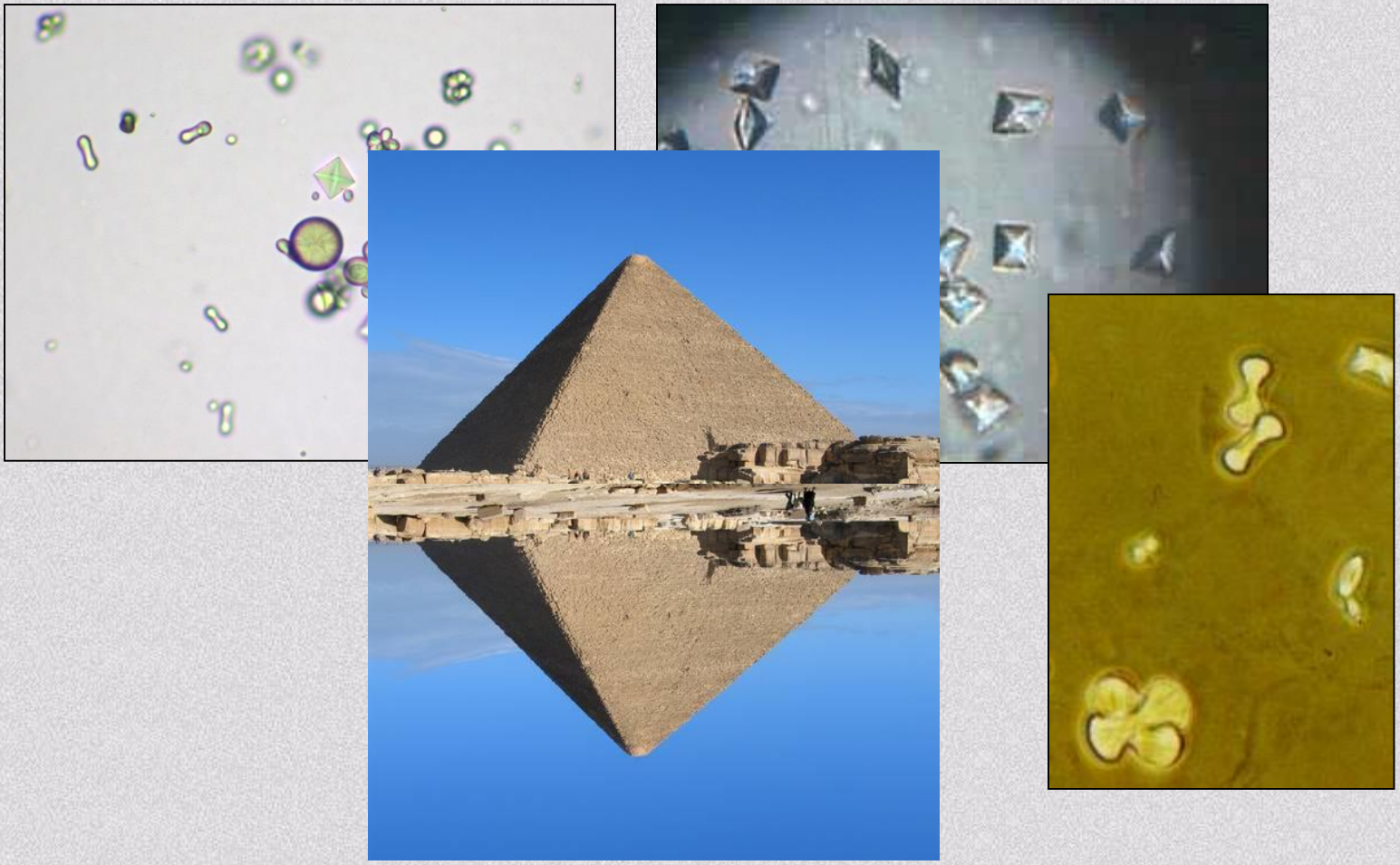
Calcium Oxalate

- Calcium-based stones are, by far, the most commonly encountered stone type
- OXALATE > PHOSPHATE
- Precipitation of the oxalate does not vary much according to pH (as opposed to the phosphate variety)

Calcium Oxalate

Calcium Oxalate



Calcium Oxalate

- HYPER-CALCIURIA
- Excess calcium in the urine can obviously increase the risk of calcium stones
- But. . . this calcium is not generally derived from the diet

Calcium Oxalate

- HYPER-CALCIURIA

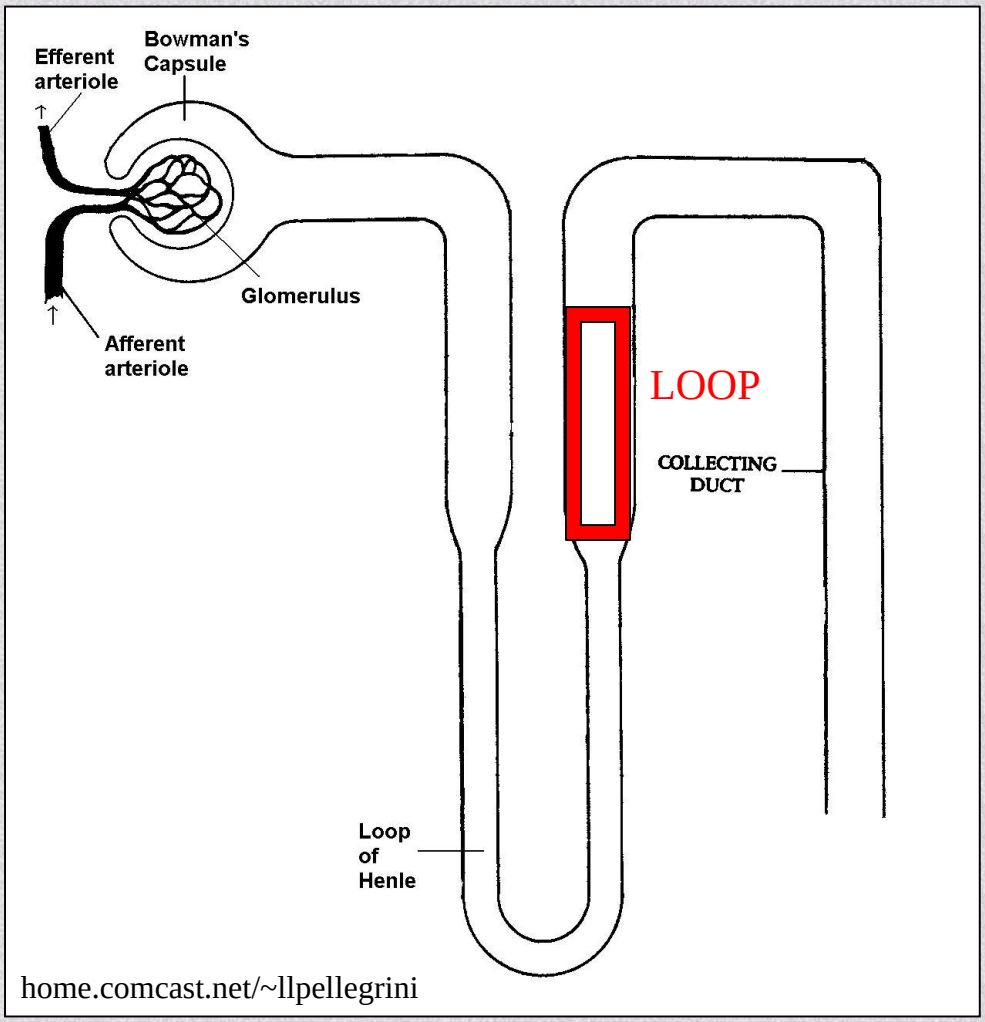
- Most of the body's calciu
  skeleton, and the amount
  (and thus the amount filte
  regulated by PTH (and Vi
- In patients prone to stone formation, restricting dietary calcium just means that the kidneys will get the calcium from somewhere else

Calcium Oxalate

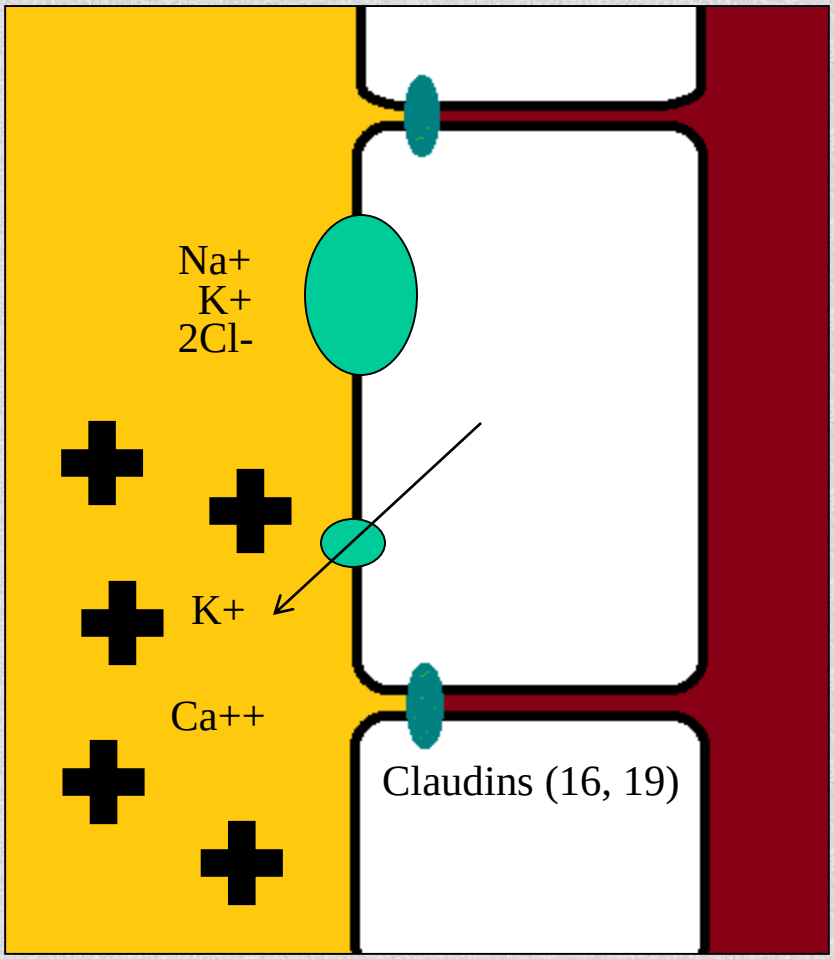
- Increases in urinary calcium can occur:

- 1) Increased serum calcium
  - Increased PTH
  - Bone resorption / turnover
- 2) Increased GI absorption
  - Excess vitamin D intake
  - Excess vitamin D production (granuloma)
- 3) Decreased renal reabsorption
  - Increased sodium excretion
  - Loop diuretics

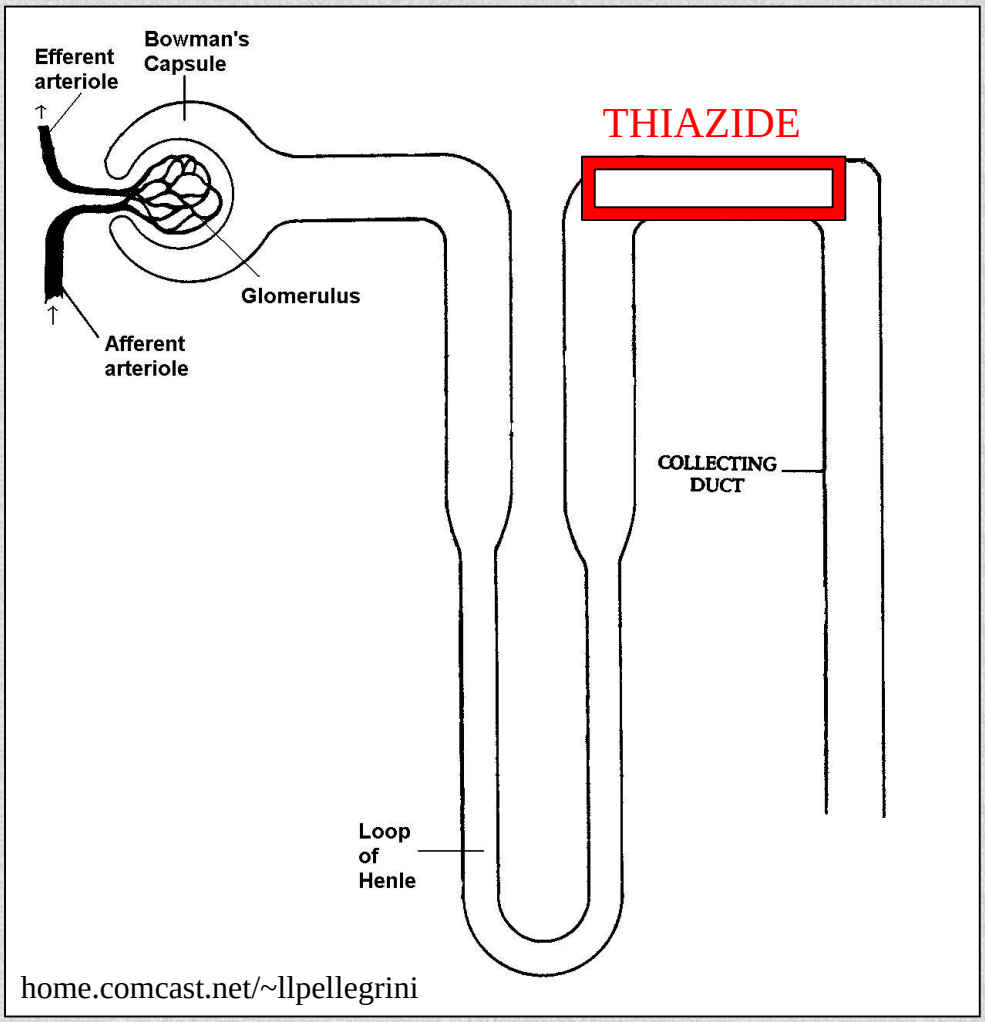
Calcium Oxalate



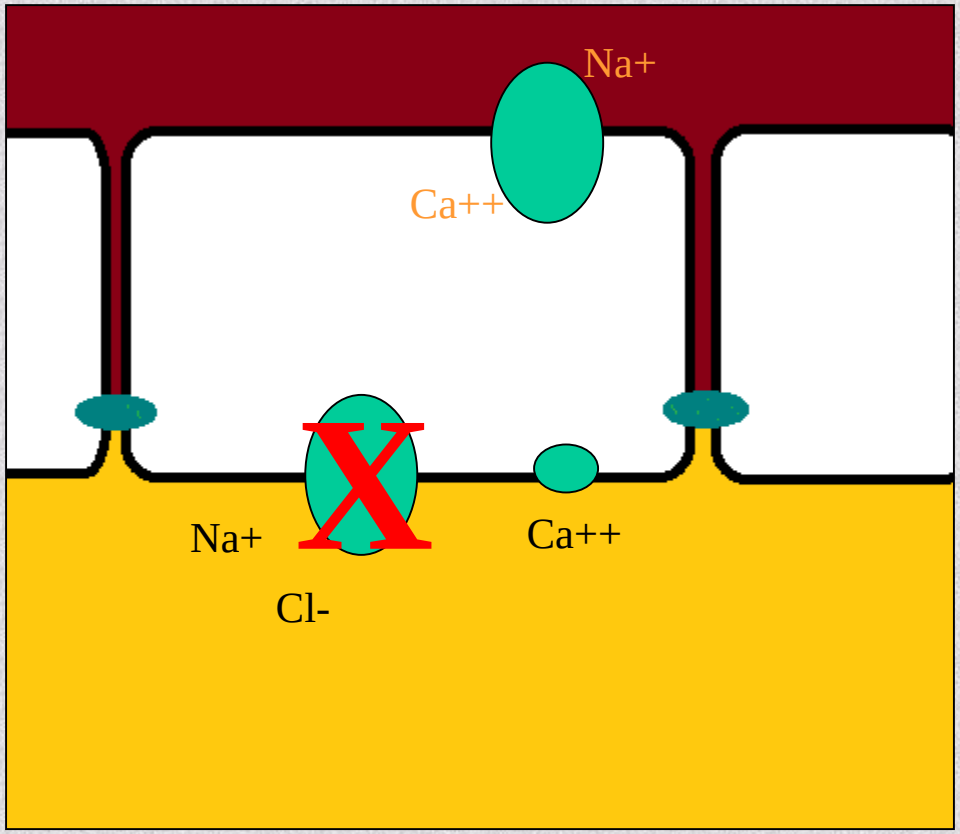
Calcium Oxalate



Calcium Oxalate



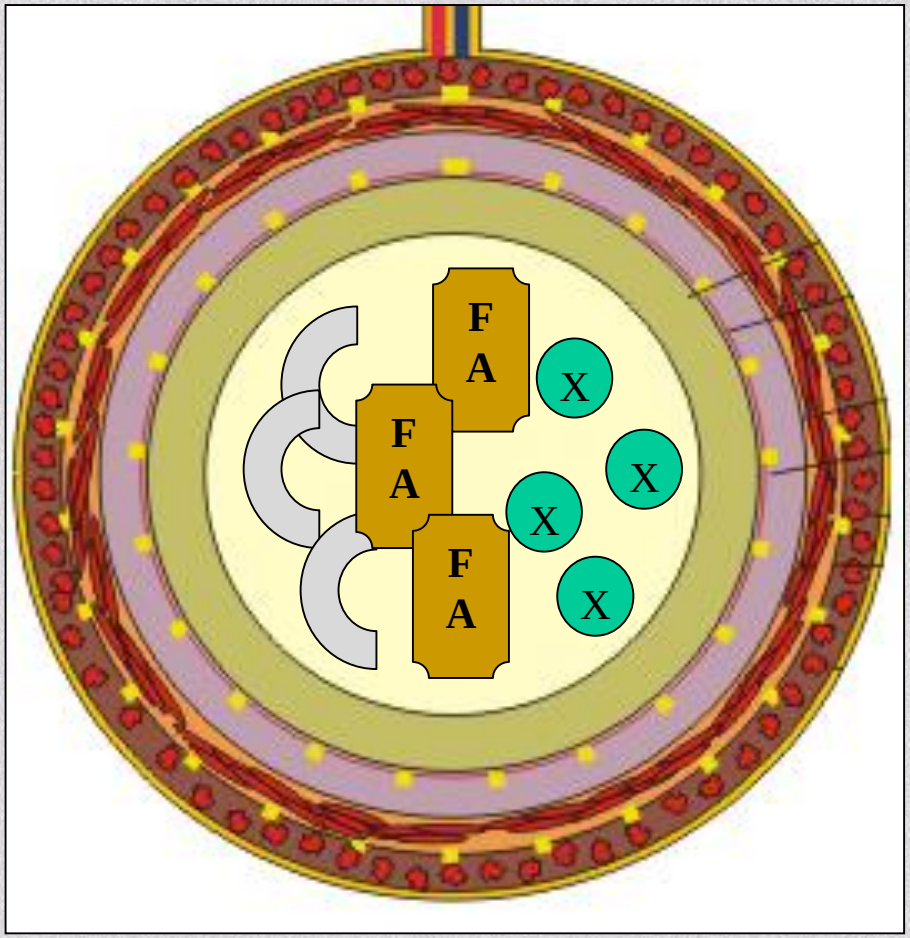
Calcium Oxalate



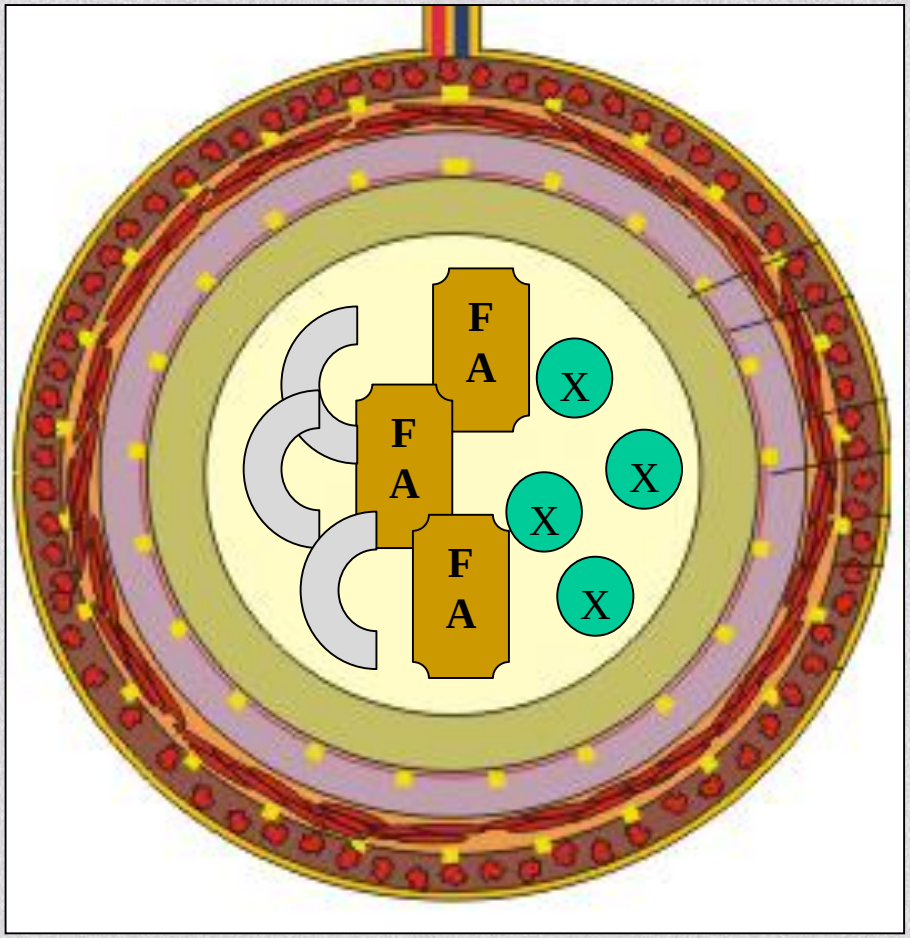
Calcium Oxalate

- HYPER-OXALAURIA
- DIET
  - Spinach, rhubarb, ch
  - Vitamin C
- GI ABSORPTION
  - Bariatric surgery
  - Fat malabsorption
- GENETIC
  - Primary hyperoxaluria

Calcium Oxalate



Calcium Oxalate



CaCO3
w/meals

Bile Acid
Sequestration

Calcium Oxalate

- HYPO-CITRATURIA
- Citrate in the urine is protective against stone formation as it binds to calcium to form a soluble complex
- HypoK can predispose to hypo-citraturia
- Supplementation with oral citrate (K-citrate, Urocit-K) can lead to conversion to bicarbonate and urinary alkalinization…

Calcium Oxalate

- HYPER-URICOSURIA

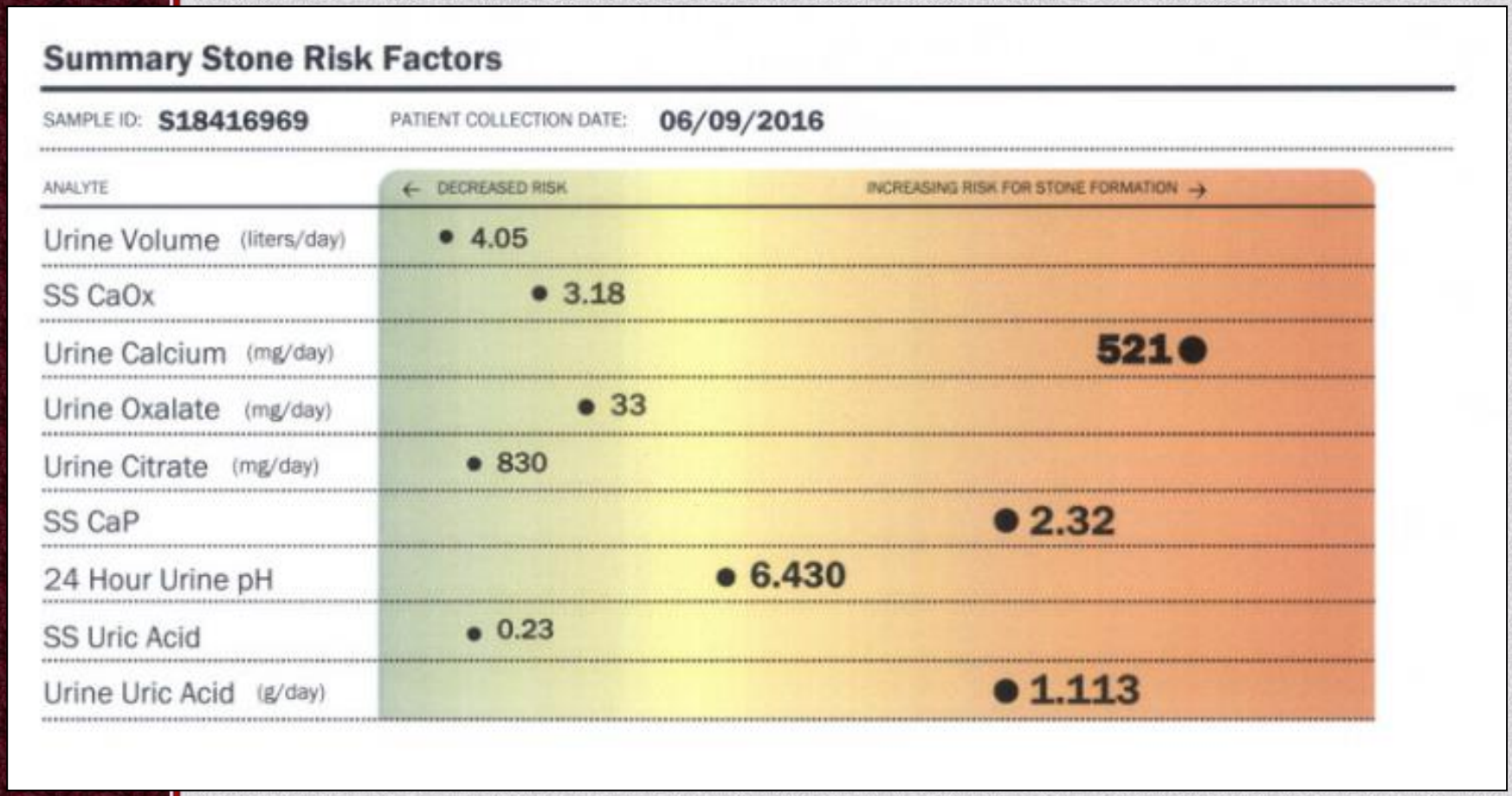
- Even in calcium-based stones, uric acid in the urine can create a nidus on which calcium salts can precipitate (heterogeneous nucleation)

- Treatment can focus on dietary purines and allopurinol

Calcium Oxalate

	Test	Result	Flag	Reference
	CREATININE, 24 HOUR URINE	1.4 G/24 HRS		1.0-2.0
	24 HOUR URINE POTASSIUM	12 mmol/24HR		7.7-91.3
	SODIUM, 24 HOUR URINE	191.4 mmol/24HR		26.4-243.8
	MAGNESIUM, 24 HOUR URINE	65 MG/24HRS		65-120
	PHOSPHORUS, 24 HOUR URINE	0.88 G/24 HRS		0.34-1.00
	URIC ACID, 24 HOUR URINE	925.6 mg/24hr	H	250.0-750.0
	CALCIUM, 24 HOUR URINE	517 mg/24hr	H	50-300
	24 HOUR URINE VOLUME	1700.0 ML/24HRS	L	>=2000.0
	URINE pH	6.0 pH		5.5-7.1
	OXALATE, 24 HOUR URINE	0.56 mmol/24 hr	H	0.08-0.49
	24 HOUR URINE CITRATE	125.6 mg/24hr	L	200.0-1000.0
	TOTAL URINE VOLUME	1700 mL		
	TIME IN MINUTES	1440 minutes		

Calcium Oxalate



Summary Stone Risk Factors

SAMPLE ID: **S18416969** PATIENT COLLECTION DATE: **06/09/2016**

ANALYTE	← DECREASED RISK — INCREASING RISK FOR STONE FORMATION →
Urine Volume (liters/day)	4.05
SS CaOx	3.18
Urine Calcium (mg/day)	521
Urine Oxalate (mg/day)	33
Urine Citrate (mg/day)	830
SS CaP	2.32
24 Hour Urine pH	6.430
SS Uric Acid	0.23
Urine Uric Acid (g/day)	1.113

Calcium Oxalate

DATE	SAMPLE ID	Vol 24	SS CaOx	Ca 24	Ox 24	Cit 24	SS CaP	pH	SS UA	UA 24
06/09/16	S18416969	4.05	3.18	521 *	33	830	2.32	6.430	0.23	1.113
REFERENCE RANGE		0.5 - 4L	6 - 10	male <250 female <200	20 - 40	male >450 female >550	0.5 - 2	5.8 - 6.2	0 - 1	male <0.800 female <0.750

Dietary Factors

DATE	SAMPLE ID	Na 24	K 24	Mg 24	P 24	Nh4 24	Cl 24	Sul 24	UUN 24	PCR
06/09/16	S18416969	316	140	152	2.442	66	305	100	25.54 *	2.2
REFERENCE RANGE		50 - 150	20 - 100	30 - 120	0.6 - 1.2	15 - 60	70 - 250	20 - 80	6 - 14	0.8 - 1.4

Normalized Values

DATE	SAMPLE ID	WEIGHT	Cr 24	Cr 24/Kg	Ca 24/Kg	Ca 24/Cr 24
06/09/16	S18416969	79.4	2596 *	32.7	6.6	201
REFERENCE RANGE				male 18-24 female 15-20	<4	<140

Calcium Oxalate

RISK FACTOR	INTERVENTION
Hyper-Oxaluria	
Hypo-Citraturia	
Hyper-Uricosuria	
Hyper-Calciuria	

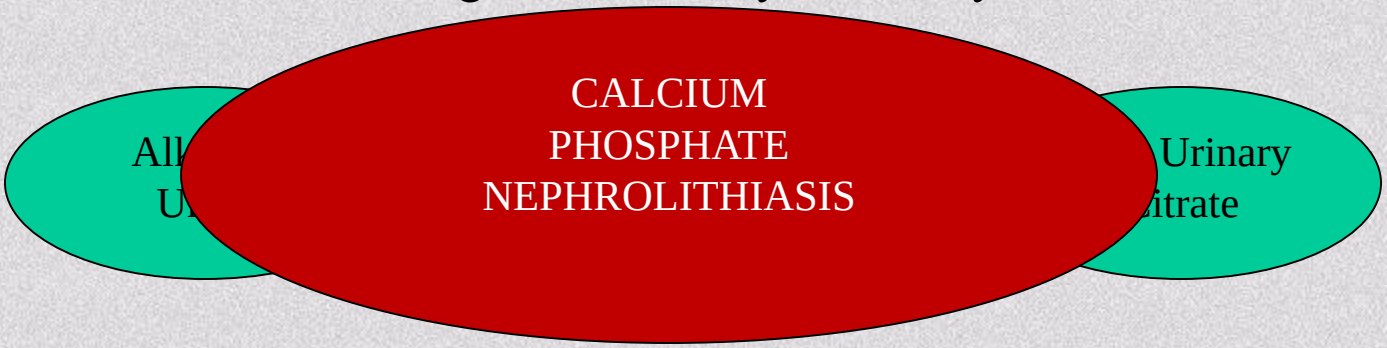
Prevention of Calcium Phosphate nephrolithiasis is essentially the same

Stone Types

- Calcium oxalate
- Calcium phosphate
- Uric acid
- Struvite ($Mg\text{-}NH_4\text{-}PO_4$)
- Cystine

Calcium Phosphate

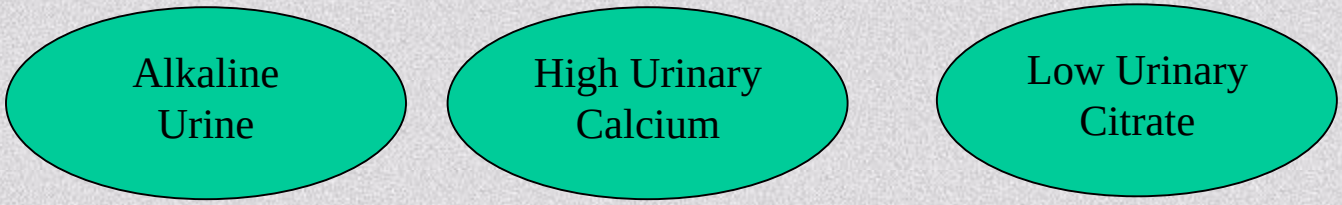
- As opposed to Calcium Oxalate stones, these are preferentially formed in ALKALINE urine
- Notably, the conditions are perfect in a DISTAL RTA, where systemic acidosis leads to:
  - Bone resorption
  - Citrate reabsorption from urine
  - And along with inability to acidify urine…



Calcium Phosphate

Calcium Phosphate

- Treatment is ALMOST the same as for calcium oxalate stones. . . just be cautious about over-alkalinizing the urine



- Urine pH should not exceed 7.0

Calcium Phosphate

- Trickier are the patients suspected of having an incomplete distal RTA
  - There is an inability to acidify the urine, tending towards a metabolic acidosis
  - However, the serum bicarbonate is normal, thanks in part to the reabsorption of citrate from the urine
  - However, there is typically profound hypocitraturia, with an already-elevated urine pH. . . the therapeutic window for citrate administration is small

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Uric Acid

- Uric acid accounts for ~5% of stones
- More than anything else, urine pH will determine the precipitation of uric acid, becoming insoluble in acidic urine, with pH<5.5
- Low urine volume is #2 on the list
- Hyper-uricosuria is not necessary for uric acid stone formation (gout, myeloproliferative disease, diet)

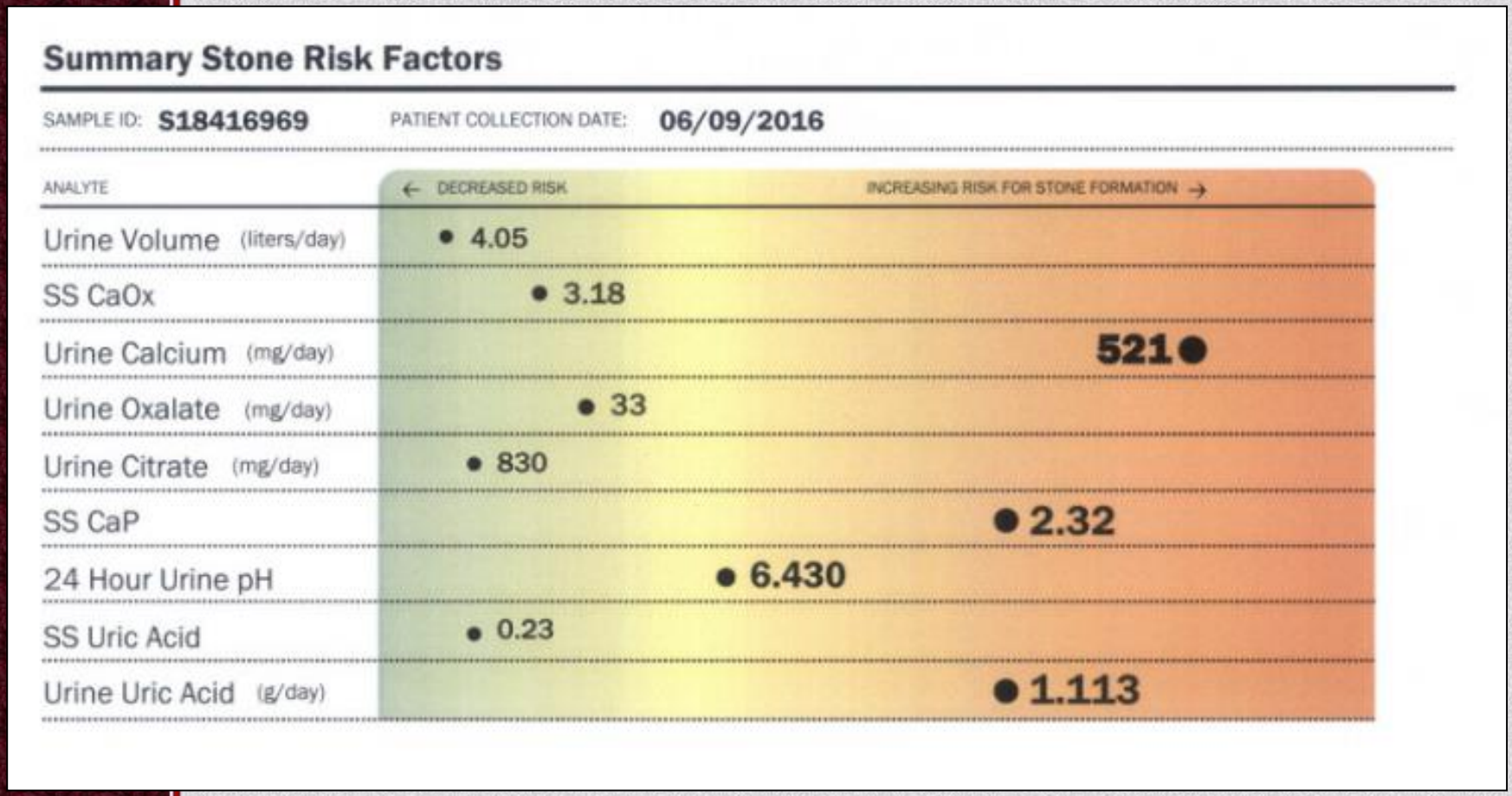
Uric Acid

These stones are notable for being RADIOLUCENT

Uric Acid

- In addition to increased fluid intake (at least 3L of UOP), urine alkalinaization is the mainstay of therapy
- Potassium citrate (10-20 mEq TID) is preferred, titrated up to a urine pH of 6.5; acetazolamide can also help alkalinize the urine
- If hyper-uricosuria is present, purine dietary restriction and allopurinol can be initiated (if above failed to work)

Uric Acid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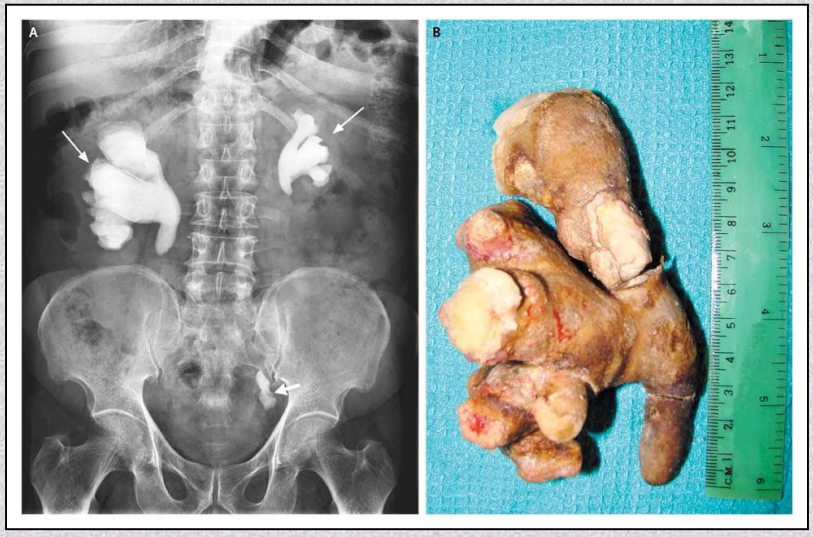
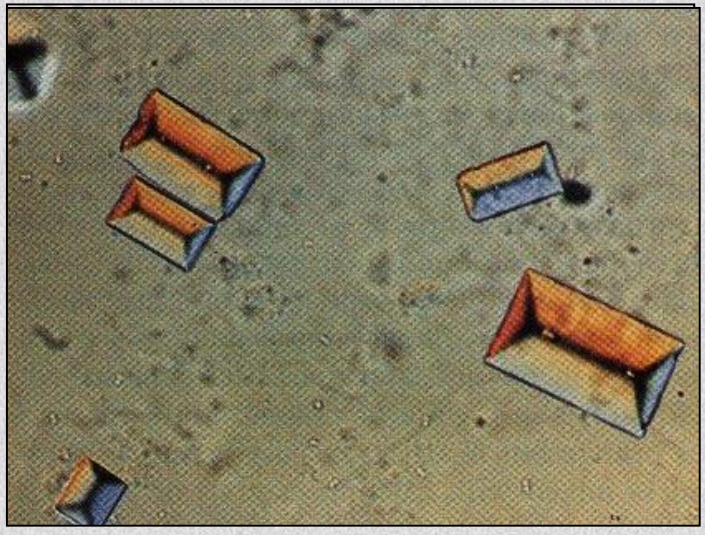
Struvite

- Struvite stones go by a variety of names
  - Struvite
  - Magnesium-ammonium-phosphate
  - “Triple phosphate”
  - Staghorn calculi



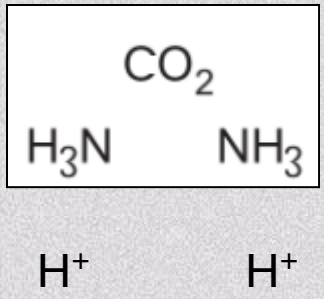


Rajaian S, Kekre NS, NEJM, 2009

Struvite

- Struvite precipitates in alkaline urine, and can be worsened by high magnesium excretion

- Strongly associated with urea-splitting organisms in urinary tract infections
  - *Proteus*
  - *Providencia*
  - *Pseudomonas*
  - *Klebsiella*
  - *Staphylococcus*
  - *Mycoplasma*



Struvite

- The bacteria produce supersaturation in their immediate surroundings, with crystallization forming around clusters of bacteria
- Treatment is typically surgical
- Bacterial eradication with abx is rare

Stone Types

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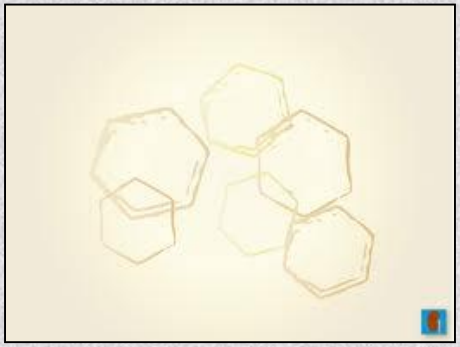
Cystine

- Cystine stones result from an autosomal recessive genetic mutation in amino acid transport (~1% of stones)



www.kidneystoners.org

- Solubility increases as pH increases (>7.0-7.5)
- At normal urine pH, 4L/day of urine would be needed to maintain solubility
- Sodium restriction to lowest possible level (U_{Na} <100 mEq/d)

Cystine

- 24-hour urine cystine is normally <75 mg/d; most cystinuric patients have levels >300 mg/d
- Sulfhydryl drugs (Thiola/tiopronin, D-penicillamine, captopril) form cross-links with cystine to increase solubility
- For patients on these medications, a cystine capacity assay may be measured (Litholink) rather than actual excretion/supersaturation

Summary

- ALL stone types can benefit from increased urine volume
- A 24-hour urine specimen is helpful in identifying risk factors (diet, meds)
- Knowing the stone type is helpful in interpreting/treating the urinary pH:
- ACID URINE: Uric Acid, Cystine
- ALKALINE URINE: CaPhos, Struvite

Question 1

- A patient with a history of calcium phosphate nephrolithiasis is diagnosed with a distal renal tubular acidosis. Which of the following is most likely to be present on the 24-hour urine specimen?
- A) Hyperuricosuria
- B) Urine pH < 5.5
- C) Hyperoxaluria
- D) Hypocitraturia
- E) Hypocalciuria

Answer 1

- Correct answer: (D)
- A distal renal tubular acidosis would lead to a systemic acidosis, resulting in bone resorption, and ultimately, hypercalciuria (not hypocalciuria). The defect in urinary acidification leads to a high urine pH. In order to attempt to correct the systemic acidosis, citrate is reabsorbed by the proximal nephron, resulting in hypocitraturia. The combination of the above factors strongly predisposes to formation of calcium phosphate nephrolithiasis. Uric acid and oxalate excretion are not typically altered in this disease state.
- Reference: Goldfarb DS. A woman with recurrent calcium phosphate kidney stones. Clin J Am Soc Nephrol. 2012;7:1172-1178

Question 2

- A patient presents with recurrent nephrolithiasis. No prior stone has been submitted for chemical analysis. Plain films of the abdomen reveal radio-opaque stones bilaterally in the area of the kidneys. Which dietary intervention is most recommended?
- A) Fluid restriction
- B) Calcium restriction
- C) Diet high in animal proteins
- D) Supplemental vitamin C
- E) Sodium restriction

Answer 2

- Correct answer: (E)
- Calcium-based stones are by far the most common and the radio-opaque stones are suggestive of this composition. Fluid intake to produce at least 2 liters of urine output is recommended, as is a diet low in sodium and animal proteins (purines). Calcium restriction was associated with INCREASED stone formation, likely related to the lack of oxalate-binding in the diet. Sodium intake, rather than calcium, is the prime determinant of calcium urinary excretion. Vitamin C supplementation is not recommended as it may be converted to oxalate and increase the risk of calcium oxalate stone formation.
- Reference: Borghi L, Schianchi T, Meschi T, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Engl J Med. 2002;346:77-84.