Nephrolithiasis

Jennifer (Howard) Jackson D.O.
Jeff Kaufhold, MD FACP
Dec 2023

Incidence

- Stones account for 7-10 per 1000 hospital admissions
- 12% of population will form a stone during their lifetime
- Men affected 2-3x more than women
- Peak onset third decade
- Highest incidence in fifth and sixth decades

Stone Composition

- Calcium oxalate alone or with apatite= 60-70%
- Pure apatite= 7%
- Brushite (calcium monohydrogen phosphate dihydrate)= 1%
- Struvite (magnesium ammonium phosphate hexahydrate)= 10-20%
- Uric acid=5-10%
- Cystine= 1-2%

Stone Composition- Rare Stones

- Xanthine stone- xanthine oxidase deficiency
- 2,8-dihydroxyadenine stones- adenine phosphoribosyltransferase deficiency
- Acid ammonium urate stones- chronic diarrhea and hypokalemia
- Oxypurinol and xanthine stones- pts taking allopurinol

Stone Composition- Rare Stones

- Triamterene stones- pts taking triamterene
- Protein “matrix” stones

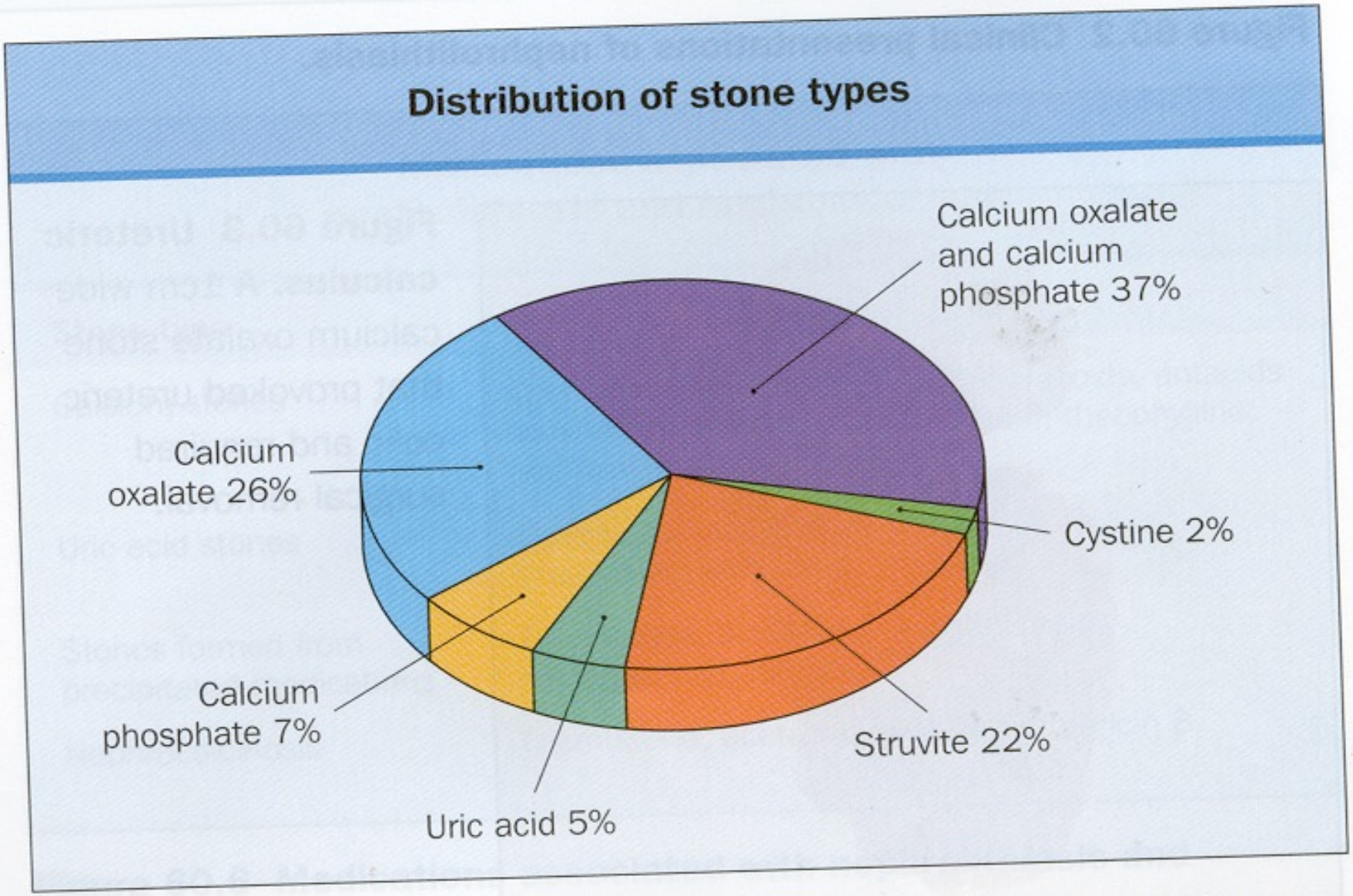
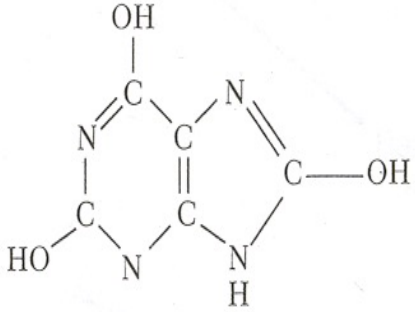
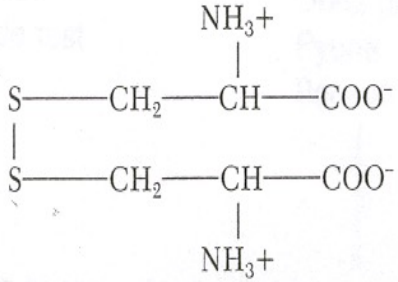


Figure 60.1 Proportion of stone types in a typical US population.

Table 55.1
Composition and Frequency of Renal Calculi

Substance	Chemical Formula	Mineral Name	Frequency
Calcium oxalate			
Monohydrate	$Ca(COO)_2 \cdot H_2O$	Whewellite	Calcium oxalate alone, 40%
Dihydrate	$Ca(COO)_2 \cdot H_2O$	Weddellite	
Apatite	$Ca_{10}(PO_4)_6(OH)_2$	Hydroxyapatite	Hydroxyapaptite alone, 7% Hydroxyapatite + calcium oxalate, 30%
	$Ca_{10}(PO_4)_6CO_3$	Carbonate apatite	
Calcium monohydrogen phosphate dihydrate	$CaHPO_4 \cdot 2H_2O$	Brushite	1%
Magnesium ammonium phosphate hexahydrate	$MgNH_4PO_4 \cdot 6H_2O$	Struvite	Struvite + carbonate apatite 10-20%
Uric acid			5-10%
Cystine			2%

Pathogenesis

- Several stages of stone formation exist
- Crystal nucleation
- Aggregation
- Attachment

Pathogenesis- Crystal Nucleation

- Supersaturation of a potentially insoluble compound
  - Increased urinary excretion
  - Reduced urinary volumes
    - Accelerated extrarenal water losses
    - Low fluid intakes

Pathogenesis- Crystal Nucleation

- Increase in urinary concentration of the compound
- Urine becomes supersaturated
  - formation product is exceeded
  - spontaneous crystal nucleation occurs
- Solubility may be affected by pH

Pathogenesis- Crystal Nucleation

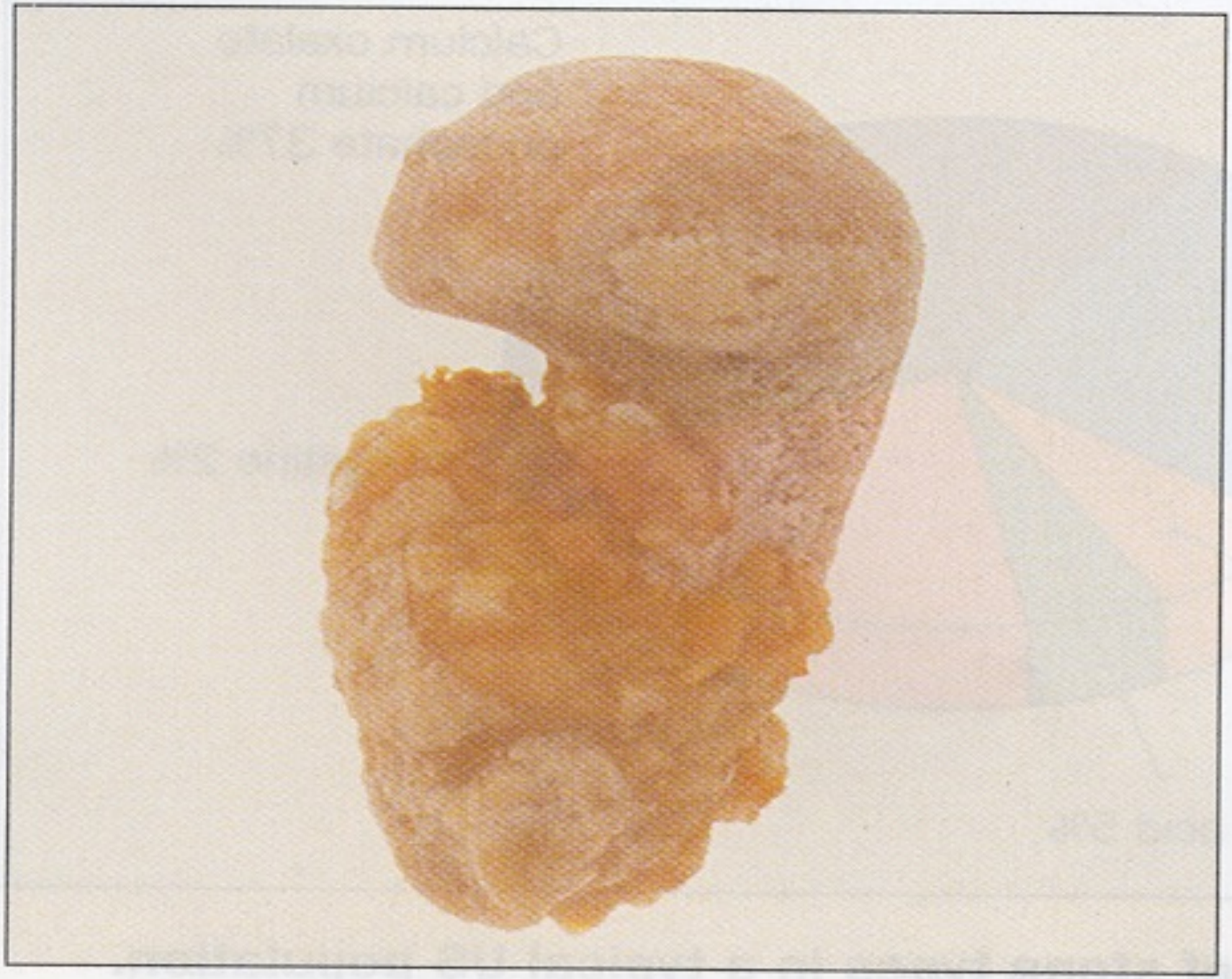
- Normal urine contains inhibitors of crystal nucleation
  - Magnesium complexes oxalate
  - Citrate complexes calcium
- Deficiency of these inhibitors increase the potential for stone formation

Pathogenesis- Aggregation

- Initial crystal nuclei aggregate with other nuclei to form larger crystals
- More likely to be retained within the kidney
- One type of stone salt my serve as nucleus for growth of another
- Ex: apatite crystal nucleus for calcium oxalate stone

Pathogenesis- Attachment

- Crystal attachment to a urinary surface is necessary to retain it in the kidney long enough to form a stone
- Often at the calyceal tips of renal papillae where they become anchored
- Cell injury may be a prerequisite



Symptoms

- Variable
- renal pelvis or upper ureter: colicky flank/abdominal pain with nausea & vomiting
- mid-lower ureter: pain radiating to inguinal ligament and labia/urethra or testicle/penis

Symptoms

- Terminal intravesicle segment of ureter: frequency and dysuria
- Ureteral colic is not exclusive to stone disease
  - Clots
  - Papillary necrosis
- Passage of stone = immediate relief

Symptoms

- Gross or microscopic hematuria may be assoc
- Painful or painless
- Large number of causes of hematuria

Causes of hematuria

Nephrolithiasis

Infection:
- cystitis, prostatitis, urethritis, acute pyelonephritis, tuberculosis, schistosomiasis

Malignancy:
- renal cell carcinoma, transitional cell carcinoma, prostatic carcinoma, Wilms' tumor

Trauma

Glomerular disease

Interstitial nephritis

Polycystic kidney disease

Papillary necrosis

Medullary sponge kidney

Coagulopathy
- bleeding disorders, anticoagulation therapy

Miscellaneous
- loin pain hematuria syndrome, arteriovenous malformation, chemical cystitis, caruncle, factitious

Figure 60.4 Causes of hematuria.

Symptoms

- Back/flank pain + F/C: obstructing stone with infection
- Renal failure
- Asymptomatic

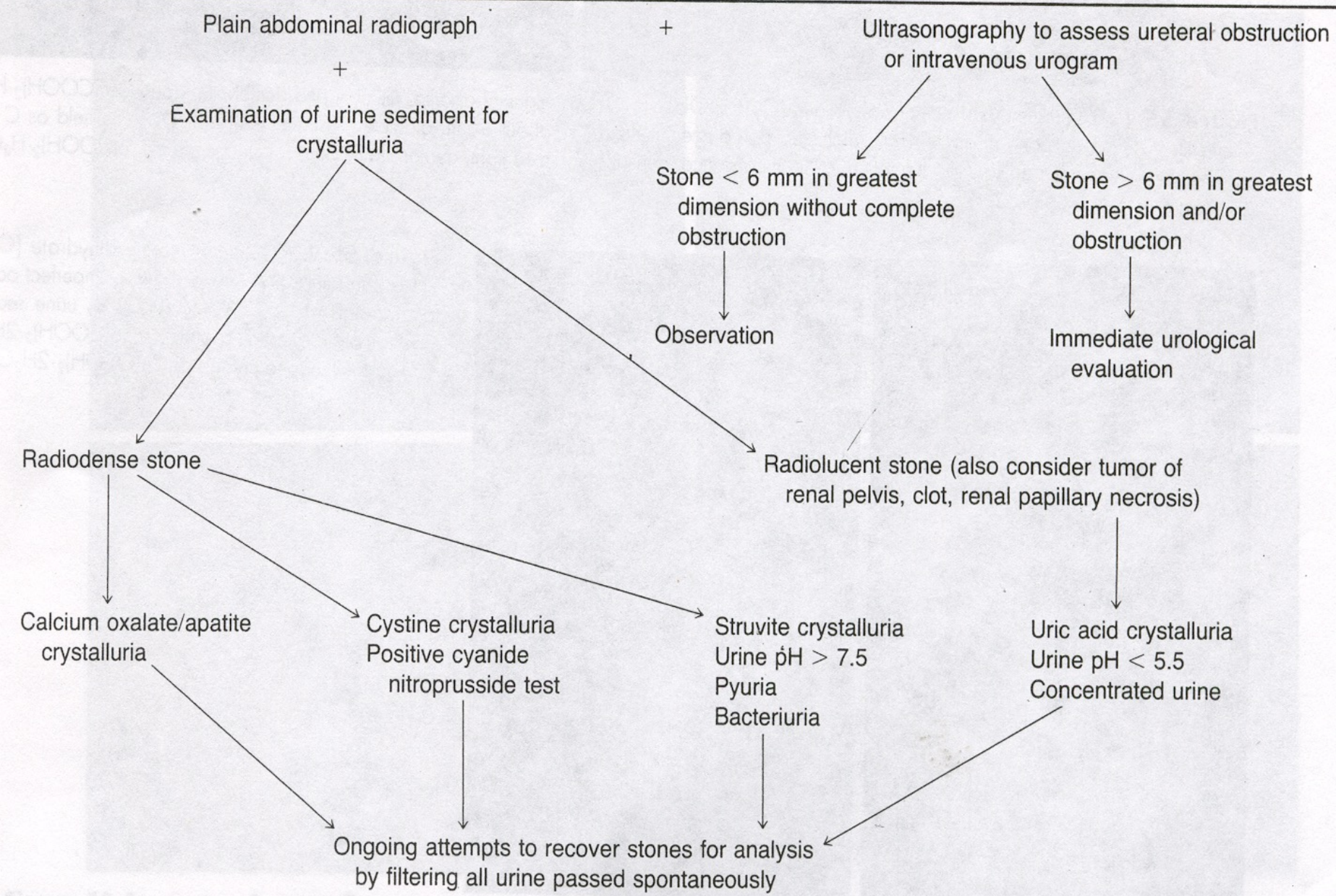
Preliminary Evaluation

- Thorough H&P
- UA with prompt microscopy for crystals
- KUB, US, or IVP to determine
  - radiolucent or radiodense
  - Number of stones, size, location
  - Presence of obstruction

Preliminary Evaluation

- Analgesics
- IV fluid if acutely ill with N&V
- Attempt to recover stones and fragments
- Collecting and straining all urine

Table 55.2
Evaluation of the Patient With Suspected Nephrolithiasis (Ureteral Colic, Hematuria, Fever)



Urologic Treatment

- Open surgery
- Extracorporeal shock wave lithotripsy
- Percutaneous nephrostolithotomy
- Ureteroscopy

Urologic Treatment

- Small stones <5mm generally pass spontaneously
- Stones >7mm, symptomatic stones in the renal pelvis, staghorn calculi require surgical intervention
- 5-7mm stones- depends on pain, infection, obstruction

Urologic Treatment

- Choice of surgical tx depends on location of stone, size, presumed composition, infection
- Lower ureter- ureteroscope
- Pelvic/upper ureteral stones- ESWL
- Percutaneous nephrostolithotomy and direct ultrasonic lithotripsy if ESWL not successful
- Large stones- combination of extracorporeal and percutaneous lithotripsy

ESWL

- Fluoroscopically focused shock waves disintegrate stone into fragments small enough to pass
- Complication include ureteral obstruction by stone fragments
- Rare bleeding and perinephric hematomas
- D/C salicylates 2 weeks prior to ESWL

Subsequent Evaluation of Stones

- Nephrolithiasis tends to recur
- Calcium oxalate stones have a 50% recurrence rate at 10 yrs
- Recurrence more frequent in men
- Prevention of recurrence requires diagnosis of cause of stone
- Need to identify metabolic abnormalities that permit stone formation
- Should do this when the acute process is over and the pt is eating normally

Evaluation of stone formers

- Basic evaluation for all stones
- Complete evaluation for
  - Recurrent stones
  - Metabolically active stones (growing in size or number per year)
  - Children
  - Noncalcium stone formers
  - Pts in groups not typically prone to stones

Typical Stone Former

- In US: Caucasians >> minorities
- Men > women
- Southeast US > Northwest US

Basic evaluation

- History and physical
- Underlying systemic illness
- Family history
- Medications
- Stone history
- Review of diet, fluid intake, occupation, and lifestyle

Basic evaluation- History

- Look for systemic etiology
- Any disease that can lead to hypercalcemia
  - Results in hypercalciuria
  - Leads to stones
- Malabsorptive GI disorders cause hyperoxaluria and can form calcium oxalate stones
- Uric acid stones in history of gout

Basic evaluation- history

- Stone history
  - Number, frequency
  - Age at incidence of first stone
  - Size of stones
  - Stone type
  - Required surgical removal?
- Indicates severity of stones and possible etiology

Basic evaluation- Family history

- Some stones may have genetic basis
  - Idiopathic hypercalciuria- AD
  - Cystinuria- AR
  - Hyperuricosuria- rare inherited metabolic disorders
  - Rare X-linked causes of calcium stones

Basic evaluation- medications

- Potentiate calcium stone formation
  - Loop diuretics- promote calcium excretion
- Uric acid lithiasis
  - Salicylates
  - Probenecid
- Some drugs precipitate into stones themselves
  - Rapidly infused IV acyclovir
  - Triamterene
  - Indinavir

Medications associated with nephrolithiasis and nephrocalcinosis	
Stone type	**Medication**
Calcium stones	Loop diuretics, vitamin D, glucocorticoids, antacids (calcium and noncalcium antacids), theophylline, acetazolamide, amphotericin B
Uric acid stones	Salicylates, probenecid, allopurinol (associated with xanthine stones)
Stones formed from precipitated medications	Triamterene, acyclovir (if infused rapidly intravenously), indinavir
Nephrocalcinosis	Triamterene, acetazolamide, amphotericin B

Figure 60.6 Medications associated with nephrolithiasis and nephrocalcinosis. (With permission from Monk[1].)

Basic Evaluation- Social History

- Occupation
  - May avoid bathroom breaks
  - Minimize fluids
- Vigorous exercise- may not rehydrate
- May lead to excessively concentrated urine and crystal precipitation

Basic Evaluation- Diet

- Diet history with each meal
  - Sodium-containing foods
  - Calcium
  - Animal protein,
  - Purine
  - Oxalate
- Fluid intake

Foods high in oxalate and purine

High-oxalate foods (avoid in setting of hyperoxaluria)	High-purine foods (avoid in setting of hyperuricosuria)
Cocoa	Organ meats: sweetbreads, liver, kidney, brains, heart
Chocolate	Shellfish
Black tea	Meat: beef, pork, lamb, poultry
Green beans	Fish: anchovies, sardines (canned), herring, mackerel, cod, halibut, tuna, carp
Beets	Meat extracts: bouillon, broth, consomme, stock
Celery	Gravies
Green onions	Certain vegetables: asparagus, cauliflower, peas, spinach, mushrooms, kidney beans, lentils
Leeks	
Leafy greens, e.g. swiss chard, spinach, mustard greens, sorrel, kale, rhubarb	
Berries: blackberries, blueberries, strawberries, raspberries, currants, gooseberries	
Orange and lemon peel	
Dried figs	
Summer squash	
Nuts, peanut butter	

Figure 60.7 Foods high in oxalate and purine.

Basic Evaluation- Physical Exam

- May uncover systemic disorder
- Tophi may be evidence for hyperuricosuria
- Paraplegia and chronic foley catheter may predispose to UTI and struvite stones

Basic Evaluation- Lab- UA

- Urine pH high: struvite and calcium phosphate stones
- Urine pH low: uric acid and calcium oxalate stones
- Specific gravity- high may show low intake
- Hematuria- active stone disease or passage
- Crystals
- Bacteria

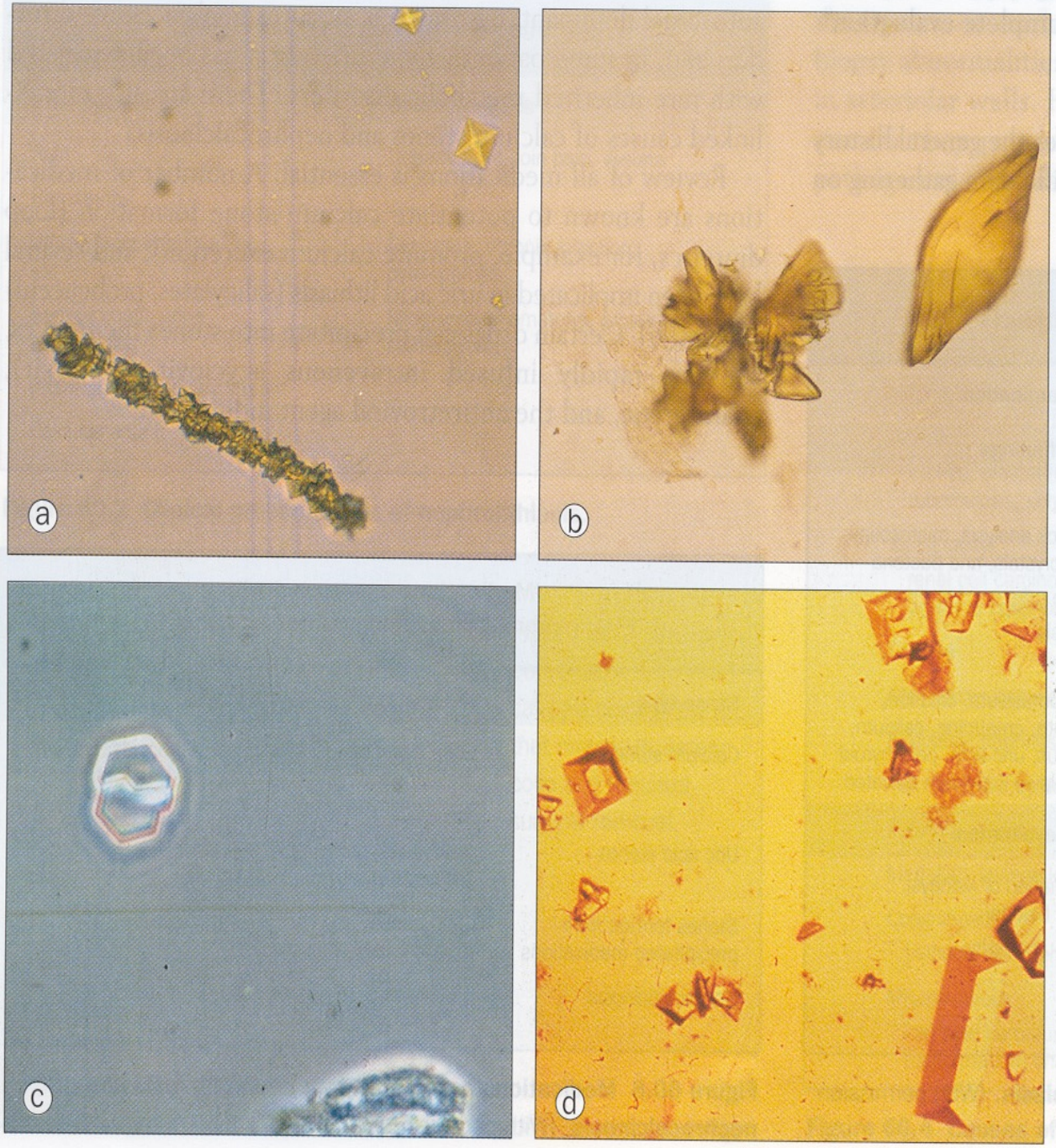


Figure 60.8 Urine crystals. (a) Oxalate crystals: a pseudocast of calcium oxalate crystals accompanied by crystals of calcium oxalate dihydrate. (b) Urate crystals: complex crystals suggestive of acute urate nephropathy or urate nephrolithiasis. (c) A typical hexagonal cystine crystal; a single crystal provides a definitive diagnosis of cystinuria. (d) Coffin lid crystals of magnesium ammonium phosphate (struvite). (Courtesy of Patrick Fleet MD).

Basic Evaluation- Lab

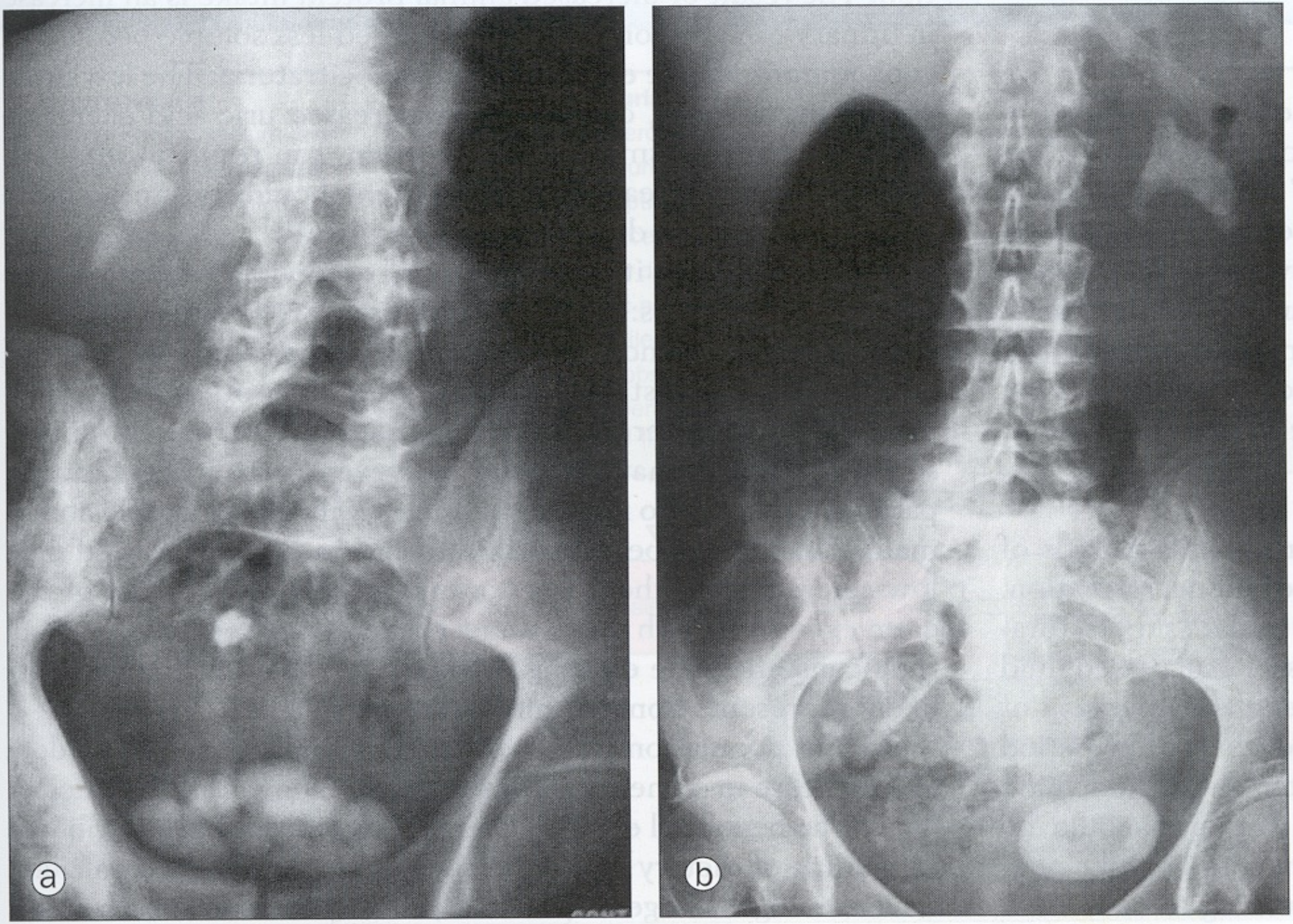
- Electrolytes
- Creatinine
- Calcium
- Uric acid
- Phosphorus
- PTH if calcium high and phos low
- Stone evaluation

Basic Evaluation- Radiologic

- IVP/IVU
  - Avoid in renal insufficiency
  - Shows obstruction
  - Shows GU abnormalities that may predispose to stone formation
  - May cause osmotic diuresis and force stone out

Basic Evaluation- Radiologic

- KUB for opacifications
  - Calcium, cystine, struvite
  - Uric acid and xanthine stones are radiolucent
- Ultrasound
  - All stones should be visible if in kidney
  - Ureteral stones may be missed
  - Good screen for pregnant women


a
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Complete Evaluation

- For special categories of stone formers
  - Recurrent stones
  - Metabolically active stones (growing in size or number per year)
  - Children
  - Noncalcium stone formers
  - Pts in groups not typically prone to stones

Complete Evaluation

- Add 24 hr urine for
  - Volume
  - Calcium, oxalate, phos, uric acid, sodium, citrate
  - Creatinine- 10mg/kg women, 15mg/kg men
- Perform on typical day
- Start after first morning void

General Treatment

- Increase in fluid intake which increases urine volume
- Sodium and animal protein restriction
- Do not restrict dietary calcium
  - May actually increase rate of stone formation

General Treatment- Fluid Intake

- Increase in urine volume to >2-2.5L/d
  - Reduces calcium oxalate supersaturation
  - Reduces precipitation of other crystals
- Mainstay of tx for uric acid and cystine stones
- Drink before bedtime and at night when up

General Treatment- Salt Intake

- Sodium excretion by renal tubules augments calcium excretion
- Salt restriction decreases sodium and calcium excretion
- Limit daily sodium intake to 3g

General Treatment- Dietary Protein

- Animal protein intake increases stones
  - Certain AA metabolism generates sulfate ions which make urine calcium less soluble
  - Causes metabolic acidosis and calcium release from bone->hypercalciuria
  - Metab acidosis causes decreased citrate excretion
  - Low urine pH + uric acid excretion = uric acid stones

General Treatment- Calcium

- Hypercalciuric pts do not have an easily identifiable disorder
- May reflect bone demineralization rather than diet
- Some studies have shown decrease in calcium stones with high calcium diet
  - Binding of dietary oxalate in the gut by ingested calcium
  - Less oxalate absorbed, less excreted by kidneys

General Treatment- Diet

- A low calcium diet is no longer recommended
- High calcium diet may be recommended
- Diet should be low protein: .8-1g/kg/day

Specific Stone Diseases

- Calcium Stones
- Oxalate stones
- Uric acid stones
- Struvite stones
- Cystine stones

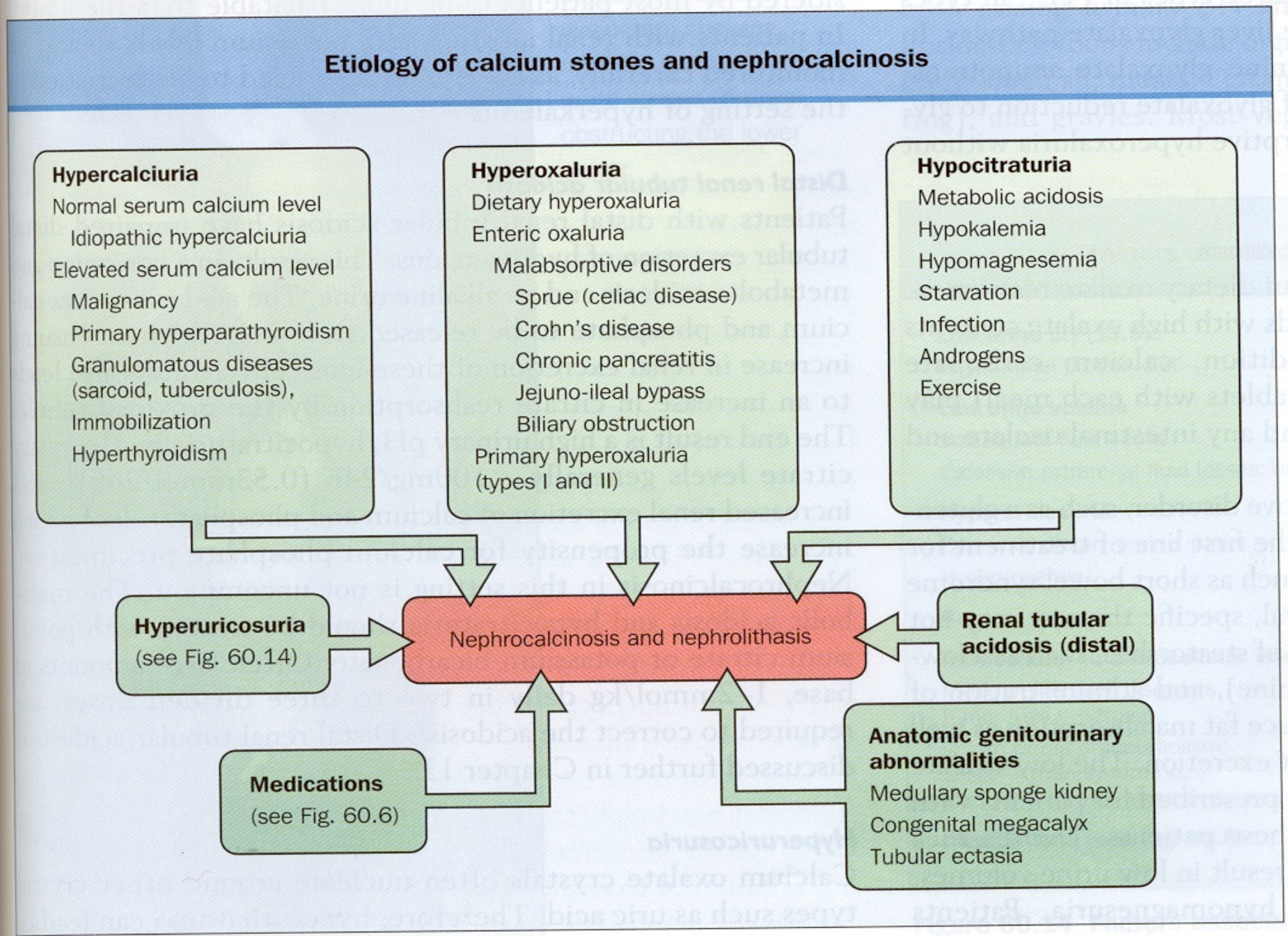
Calcium stones

- Most common stones- 70%
- Most are calcium oxalate +/- phosphate or urate
- Small percentage entirely calcium phosphate
- Most <1-2 cm

Calcium stones

- May be due to
  - Hypercalciuria, hyperoxaluria, Hyperuricosuria
  - hypocitraturia
  - RTA
  - Meds
  - GU congenital anomalies
- Specific therapy aimed at underlying metabolic disorder

uria is associated with a variety of other abnormalities". In Dent's



Hypercalciuria

- Usually idiopathic hypercalciuria
  - Isolated excess of urine calcium
  - No other abnormality of calcium metabolism or transport
- Uncommon recessive variants assoc with other abnormalities

Hypercalciuria- Treatment

- First line tx is thiazide diuretic
  - Chlorthalidone 25-50mg is drug of choice- QD
  - Indapamide does not raise serum lipids
- Increase potassium intake and watch K
- Potassium citrate preferred as supplement because citrate is also stone inhibitor
- Urocit-K is pill form- more palatable

Hypercalciuria- Treatment

- Watch K and bicarb- citrate is a base
- Check 24 hr urine calcium, sodium, citrate after several weeks
  - if urine calcium excretion still high, limit sodium intake further
  - better response to the diuretic
- If K stays low, may need to add amiloride

Hyperoxaluria

- Excessive dietary intake
  - Levels usually <60mg/24hrs
- GI disorders with malabsorption
  - Excessive oxalate absorption
  - Sprue, crohn's, chronic pancreatitis, short gut
- Inherited enzyme def with excessive metabolism of oxalate
  - Primary hyperoxaluria Type 1.
  - Infiltrate of calcium oxalate into organs

Hyperoxaluria- Treatment

- Dietary oxalate restriction
- Calcium carbonate 2-3 with meals to bind intestinal oxalate and prevent absorption
- Treat specific malabsorption syndrome
- PH- treatment is liver transplant to replace defective enzyme
  - Keep urine pH >6.5 to maintain calcium and oxalate more soluble

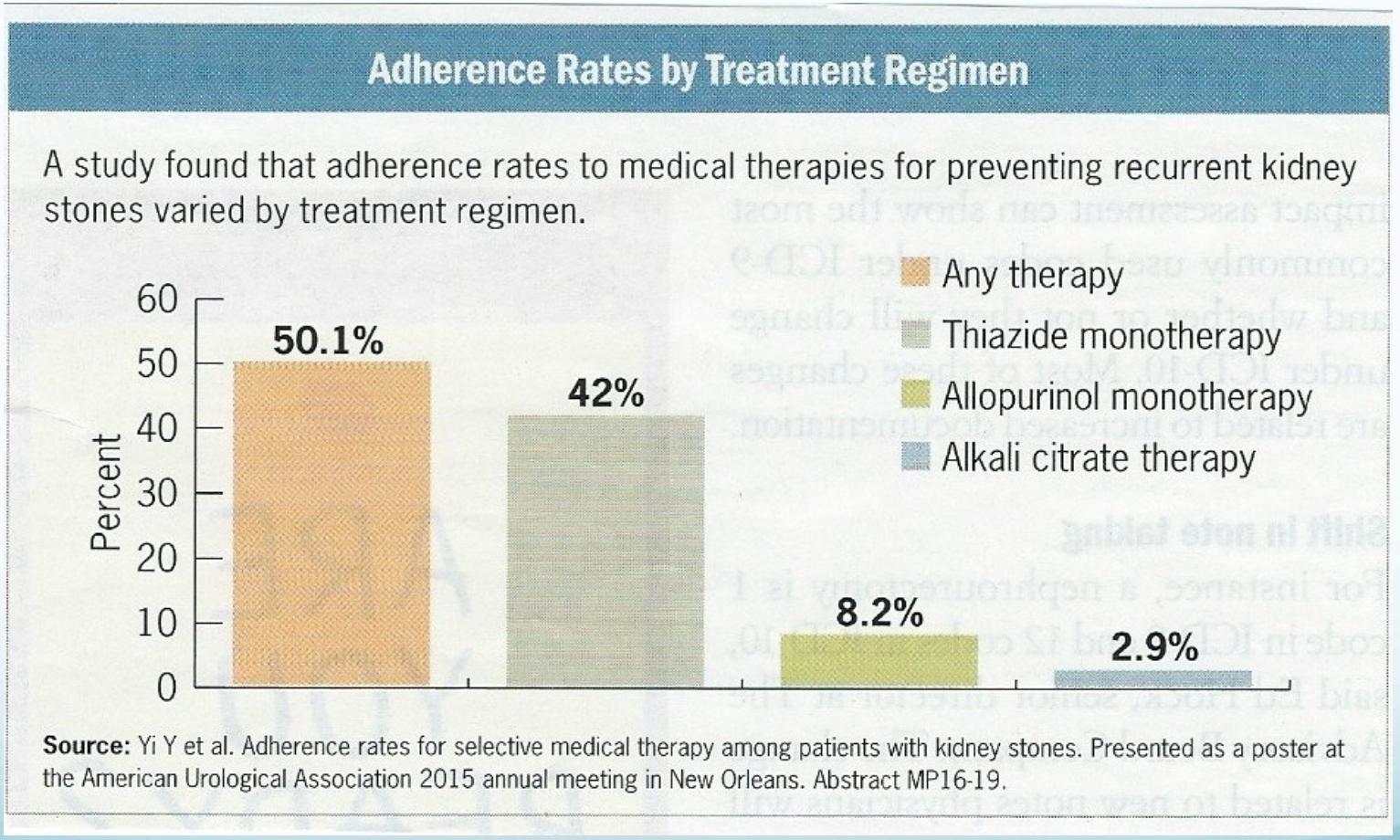
Hyperoxaluria- Treatment

- Primary Hyperoxaluria type 1
  - Age 9 years and older with Genetic mediated disease
  - New treatment is Nedosiran (Rivfloza, Novo nordisk)
  - Subcutaneous injection monthly
    - 80-128, or 160 mg doses
    - RNA interference therapy
    - Interferes with liver synthesis of oxalate
    - Available 2024
    - Based on PHYOX3 study Oct 2 2023.

Hypocitraturia

- Citrate inhibits stone formation
- Inhibits urinary citrate excretion: hypokalemia, metabolic acidosis, exercise, hypomagnesemia, infection, androgens, starvation, acetazolamide
- Tx: treat underlying disorder and add potassium citrate supplements

Compliance with stone treatment



Distal RTA

- Impaired distal tubular excretion of hydrogen ions
- Non-anion gap metab acidosis and alkaline urine
- Acidosis causes
  - calcium & phos release from bone, incr renal excretion
  - Increased citrate reabsorption in proximal tubule
- Increasing risk for calcium phosphate precipitation
- Treat with potassium citrate or potassium bicarb

Hyperuricosuria

- Calcium oxalate crystals nucleate around uric acid crystals
- May have normal urinary calcium and oxalate levels
- Higher urinary pH >5.5
- Tx: increased fluid intake, low purine diet
- May need allopurinol

Uric Acid Stones

- Prevalence depends on geographic location
- US- 5-10%
- Radiolucent
- Seen on US and CT
- Filling defects on pyelography

Factors associated with uric acid stones

Low urine pH (≤5.5)

High animal protein diet

Low urine volume

Inadequate fluid intake

Excessive extrarenal fluid losses: diarrhea, insensible losses (perspiration, etc.)

Hyperuricosuria

Excessive dietary purine intake

Hyperuricemia

Gout

Intracellular to extracellular uric acid shift

Myeloproliferative disorders,
tumor lysis syndrome

Inborn errors of metabolism:
Lesch–Nyhan syndrome,
glucose 6-phosphatase deficiency

Medications (see Fig. 60.6)

Figure 60.14 Factors associated with uric acid stone formation.

Uric Acid Stones

- Hyperuricosuria due to
  - Excessive dietary purine or protein intake
  - abnormal cellular breakdown (tumor lysis, hemolysis, myeloproliferative synd)
  - gout
  - uricosuric meds
  - inborn errors of metabolism

Uric Acid Stones

- Stone formation due to
  - Low urine pH
  - Low urine volume
  - Elevated urinary uric acid levels

Uric Acid Stones

- Treatment
  - Increase urine volume >2.5L/d and pH
  - Decrease uric acid excretion- K Citrate, acetazolamide
  - Target urine pH 6.5-7
  - Low purine, low animal protein diet
- If uric acid excretion still high, allopurinol

Struvite Stones

- Aka infection or triple phosphate stones
- Grow rapidly to large size
- Can reduce renal function
- Cause most staghorn calculi (penetrate more than one renal calyx)
- Formed by presence of urease-producing bacteria in urine

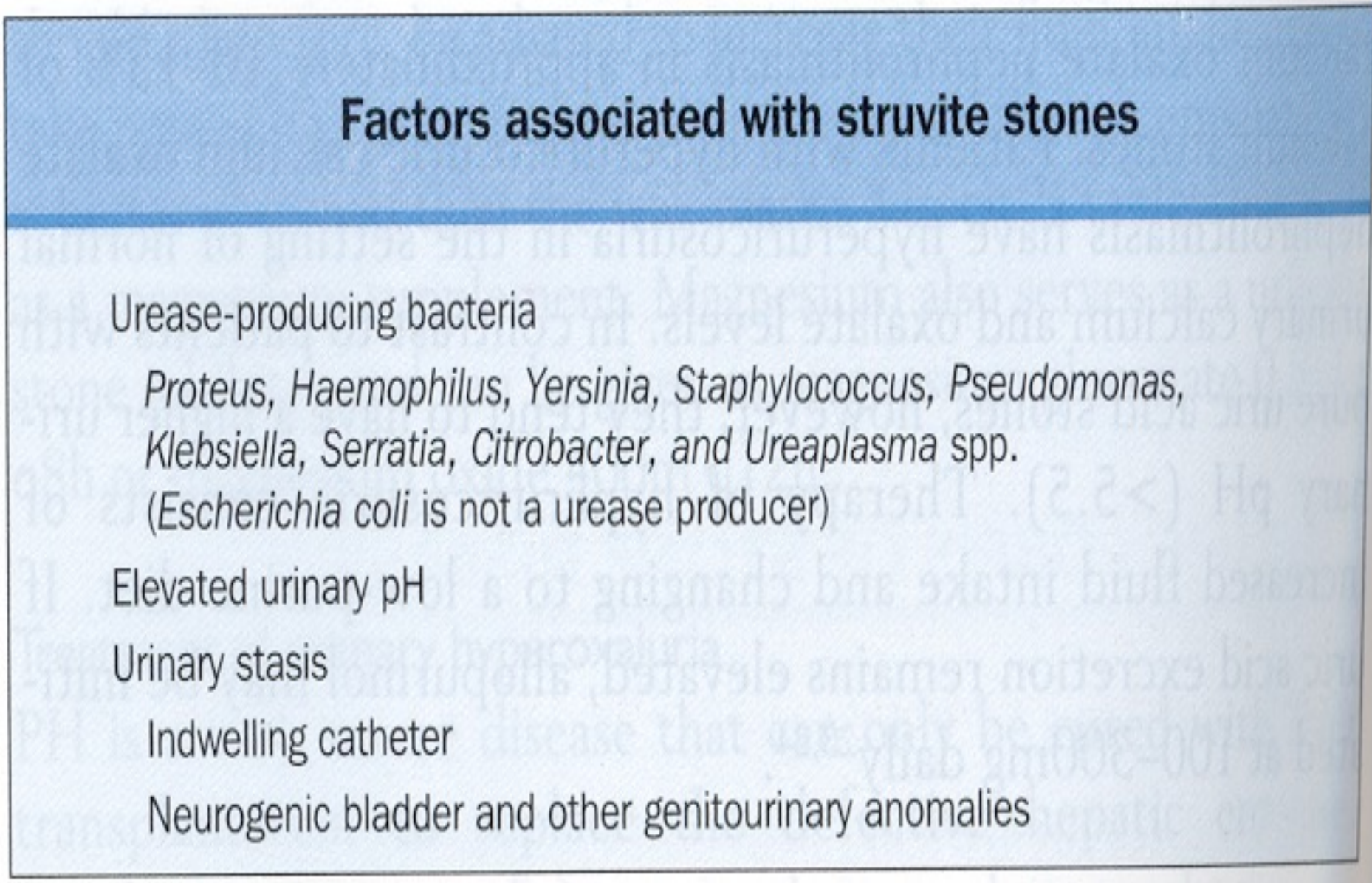


Figure 60.15 Factors associated with struvite stone formation.

Struvite Stones

- Women > men
- Indwelling catheters, neurogenic bladders, GU anomalies
- Urease production by bacteria results in
  - formation of ammonium ions and alkaline urine
  - phosphate combines with ammonium, magnesium and calcium

Struvite Stones

- Urease production occurs even with small numbers of colonies
- If culture neg, do special cx for ureaplasma urealyticum
- Requires aggressive medical and surgical tx
- Tx: abx with chronic suppression until stones completely gone
- Need stone removal for cure- early urologic referral

Struvite Stones

- ESWL, percutaneous nephrostolithotomy or combination may be required
- Adjunct tx- urease inhibitors
  - Numerous side effects
  - Not used in renal insufficiency
- Chemolysis
  - Irrigation of kidney via nephrostomy tube or ureter with solution to dissolve the stone

Cystine Stones

- Cystinuria is a rare hereditary disorder
  - tubular defect in dibasic amino acid transport
  - Increased cystine, ornithine, lysine and arginine excretion
- Stones seen by fourth decade
- Staghorn or multiple bilateral stones

Cystine Stones

- Tx: decreasing urinary cystine concentration
- Increase urine volume, sometimes up to 4L per day
- D-penicillamine and tiopronin bind cystine
  - side effects – GI upset
  - Expensive but tiopronin part of orphan drug program

Summary

- Kidney stones are common
- Symptoms range from renal colic with gross hematuria to obstruction with infection to asymptomatic
- Evaluate every stone former with a basic workup
- Unusual patients should have complete workup

Summary

- Most stones contain calcium
- Increase urine volume with fluids
- Decrease dietary sodium and animal protein
- Low calcium diet no longer recommended
- Uric acid stones are radiolucent
- Struvite stones are infectious and need removal
- Cystine stones are rare

The End

Thank you for coming-
Have a nice day!

Renal Calculi

Renal Calculi develop by precipitation of soluble salts in the collecting tubule or connecting tubule of the urinary tract

The formation of calculi is related to

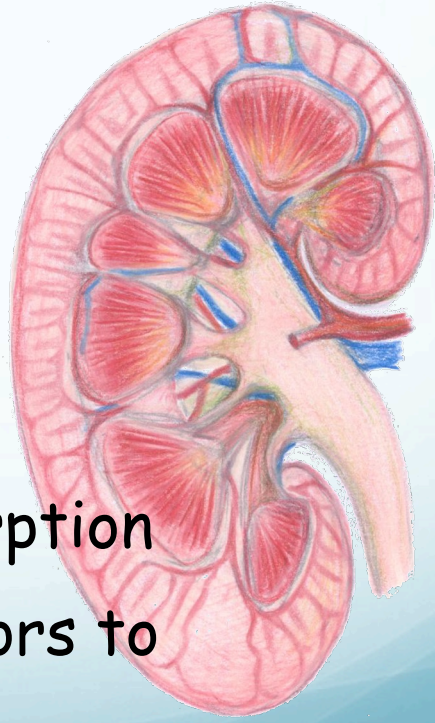
-impairment of the metabolism

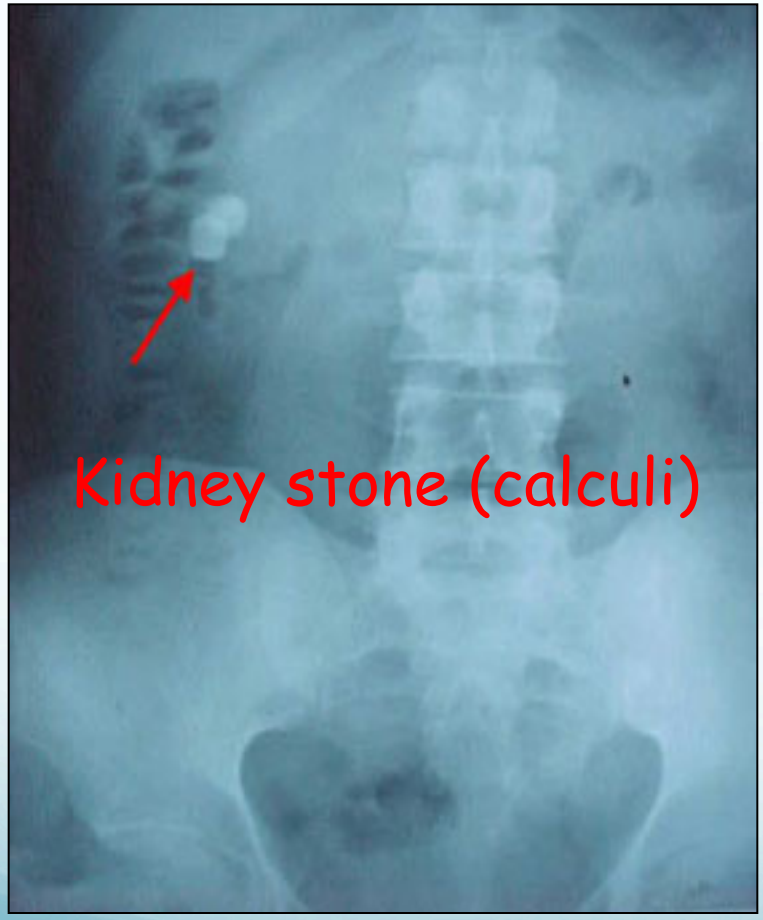
(overproduction of metabolites)

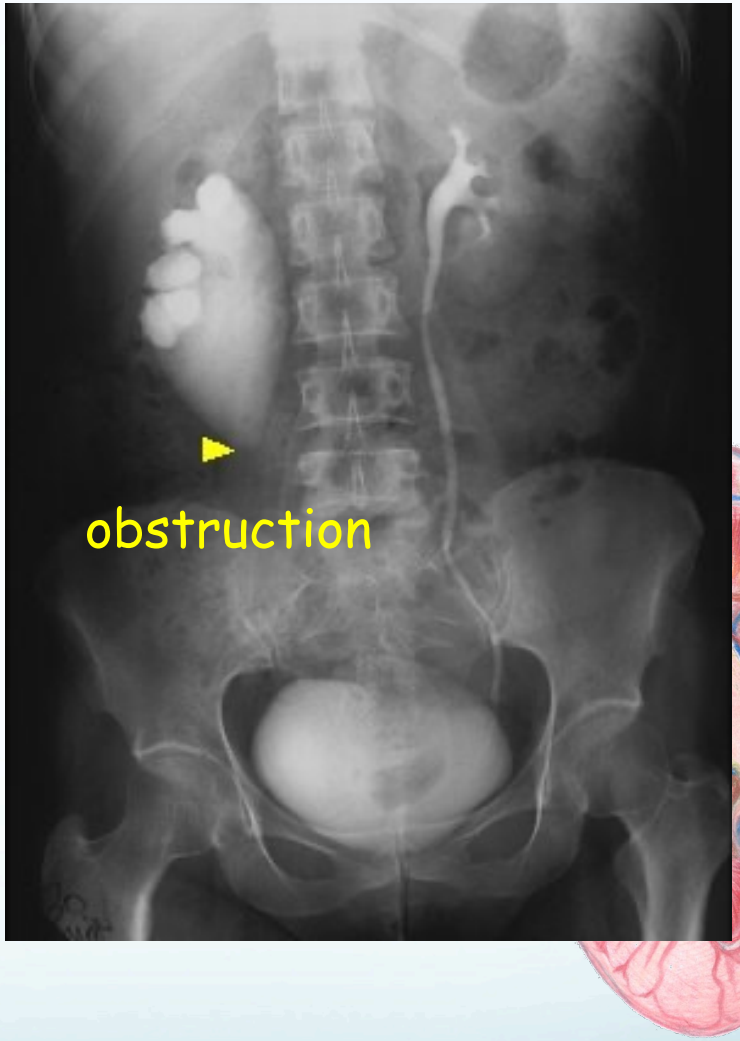
→ filtration thresholds are exceeded!

-Impairment of renal filtration or re-absorption

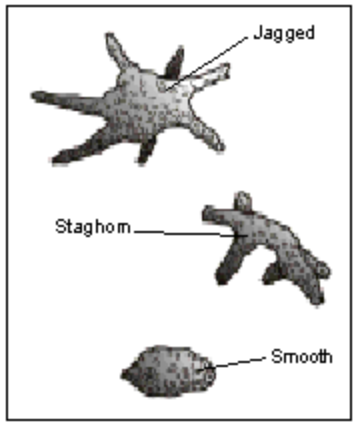
-Impairment of renal production of inhibitors to stone formation.




Kidney stone (calculi)


obstruction

Renal Calculi

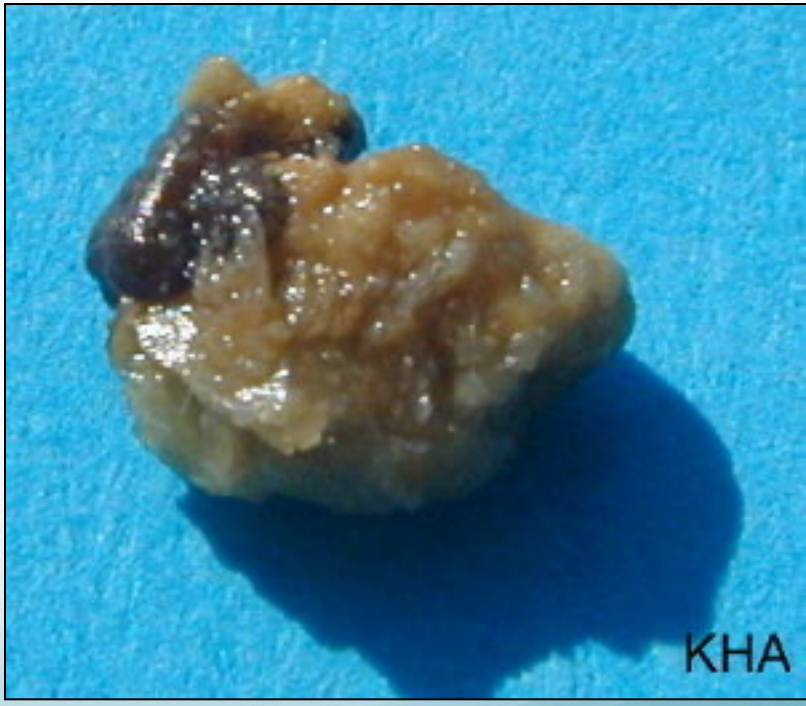


Types

Composition	%	Radio-opaque	Appearance	Pathogenesis
Calcium oxalate	60	+++	Small, smooth or spiky	Hyperparathyroidism, hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria
Calcium phosphate	20	+++	Slightly larger more friable	Distal renal tubular acidosis
Uric acid	<10	-	May be large	Low urinary pH, Hyperuricosuria
Struvite	<10	++	Staghorn	Infection with urease-producing microorganisms
Cystine	<5	+	Pale yellow, may be large	Cystinuria

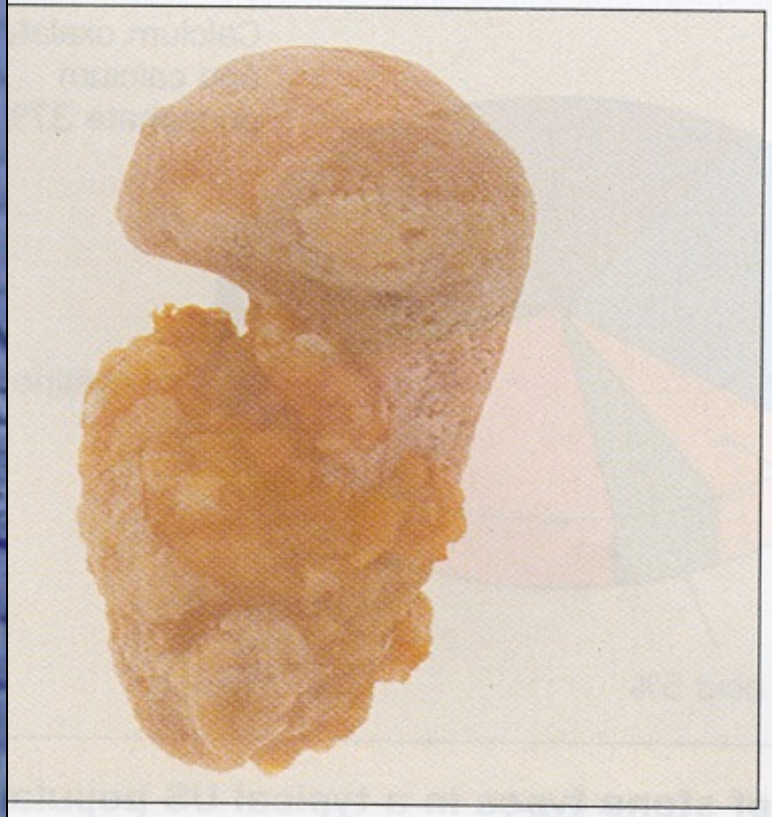
Urate stone

Cystine Stone



Calcium Oxalate stone

Calcium Oxalate stone
Formed on a Urate Nidus

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